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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

THIRTEENTH SESSION,

HELD AT WASHINGTON, D. C.,

MAY 3, 4, AND 5, 1898.

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1886.	SCHMIDT, H. D., M.D., New Orleans.
1886.	THACHER, JAMES K., M.D., New Haven, Conn.

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MINUTES

OF THE

THIRTEENTH ANNUAL MEETING,

Held in Washington, D. C., May 3, 4, *and* 5, 1898.

The following members were present during the meeting:

A. C. Abbott.	C. F. Folsom.	William Osler.
John S. Abel.	F. Forchheimer.	T. M. Prudden.
J. F. A. Adams.	M. H. Fussell.	F. C. Shattuck.
Isaac Adler.	J. E. Graham.	G. B. Shattuck.
I. E. Atkinson.	J. P. C. Griffith.	A. H. Smith.
G. Baumgarten.	I. M. Hays.	Theobald Smith.
H. M. Biggs.	H. Hun.	M. A. Starr.
B. M. Bolton.	H. M. Hurd.	G. M. Sternberg.
S. C. Busey.	A. Jacobi.	D. D. Stewart.
W. T. Councilman.	E. G. Janeway.	C. G. Stockton.
E. G. Cutler.	W. W. Johnston.	W. S. Thayer.
W. H. Draper.	F. P. Kinnicutt.	W. H. Thomson.
H. C. Ernst.	T. S. Latimer.	James Tyson.
R. H. Fitz.	M. J. Lewis.	V. C. Vaughan.
W. E. Fischel.	S. J. Meltzer.	H. P. Wolcott.
S. Flexner.	J. H. Musser.	William H. Welch.

TUESDAY, MAY 3D—MORNING SESSION.

The President, Dr. F. C. Shattuck, called the Association to order at 10.20 A.M., and delivered

THE PRESIDENT'S ADDRESS.

(See page 1.)

The minutes of the last meeting of the Association were accepted as printed in Volume XII. of the *Transactions*.

The Treasurer read his annual report, which was referred to an Auditing Committee, consisting of Drs. A. H. Smith, and C. G. Stockton.

Dr. S. J. Meltzer read a paper entitled "Congenital Stenosis of the Pylorus," which was discussed by Drs. Adler, Jacobi, and Meltzer.

Dr. D. D. Stewart read a paper entitled "Gastric Carcinoma associated with Hyperchlorhydria," which (the privilege of the floor having been accorded to Drs. Max Einhorn and Hammeter by vote of the Association) was discussed by Drs. Fischel, Welch, Hammeter, Tyson, F. C. Shattuck, Johnston, Kinnicutt, Janeway, Stockton, A. H. Smith, and D. D. Stewart.

Dr. Flexner read a paper entitled "Gastric Syphilis, with the Report of a Case of Perforating Syphilitic Ulcer of the Stomach," which was not discussed.

Dr. Adler read a paper entitled "Some Observations on Cardiac Syphilis," which was not discussed.

Dr. Janeway read a paper entitled "Danger of Error in Diagnosis between Chronic Syphilitic Fever and Tuberculosis," which was discussed by Drs. Atkinson, Meltzer, Kinnicutt, Stockton, Vaughan, Tyson, Janeway, and Cutler.

The Association adjourned at 1.30 P.M.

Afternoon Session.

The President, Dr. Shattuck, called the meeting to order at 2.50 P.M.

Dr. Thayer read a paper entitled "Nephritis of Malarial Origin," which was discussed by Drs. Forchheimer, Osler, Jacobi, Atkinson, Tyson, Fussell, and Thayer.

Dr. Councilman read a paper entitled "Acute Interstitial Nephritis," which was discussed by Drs. Welch, Tyson, and Councilman.

Dr. Fitz read a paper entitled "The Significance of Albumosuria in Medical Practice," which was discussed by Drs. Vaughan and Fitz.

The Association adjourned at 4.30 P.M.

Wednesday, May 4th—Morning Session.

The President, Dr. Shattuck, called the meeting to order at 10.15 A.M.

Dr. Sternberg read a paper entitled "Bacillus Icteroides (Sanarelli), and Bacillus X (Sternberg)," which was discussed by Drs. Abbott, Vaughan, Osler, and Sternberg.

Dr. Theobald Smith read a paper entitled "Comparative Studies of Bovine Tubercle Bacilli and of Human (Sputum)" which was discussed by Drs. Abbott, T. Smith, and Osler.

Dr. Flexner read a paper entitled "Pseudo-tuberculosis Hominis Streptotricha," which was not discussed.

Dr. Meltzer read a paper, written by himself and Dr. Cheesman, entitled "An Experimental Study of the Inoculation of the Spleen with Micro-organisms, and a Contribution to our Knowledge of the Lesion of a Body-tissue for the Settlement and Development of Bacteria within it," which was discussed by Drs. Welch, Jacobi, and Meltzer.

Dr. Fussell read a paper, written by himself and Dr. Taylor, entitled "Acute Leucæmia," which was discussed by Drs. Osler, Janeway, Shattuck, and Fussell.

Dr. Osler read a paper entitled "Paralysis of the Left Recurrent Laryngeal Nerve in Mitral Stenosis," which was not discussed.

The Association adjourned at 1.22 P.M.

Afternoon Session.

The President, Dr. Shattuck, called the meeting to order at 2.45 P.M.

Dr. Janeway read a paper entitled "Two Attacks of Temporary Hemiplegia Occurring in the same Individual as the Result of the Use of Peroxide of Hydrogen in a Sacculated Empyema (Pleural)," which was discussed by Drs. Meltzer, Hun, Fitz, and Janeway.

The discussion on "Is a Uric-acid Diathesis an Important Factor in Pathology?" was opened by Dr. Vaughan, representing physiological chemistry; by Drs. Draper and Tyson, representing clinical medicine, and was continued by Drs. C. A. Herter, A. H. Smith, Stockton, Jacobi, Vaughan, Draper, and Tyson.

Dr. J. H. Wright, of Boston, gave a demonstration by lantern-slides of a case of Madura foot.

Dr. H. C. Ernst gave a lantern-slide demonstration of microscopic color-photography.

The Association adjourned at 5.45 P.M.

Thursday, May 5th—Morning Session.

The President, Dr. Shattuck, called the meeting to order at 10.20 A.M.

Nominations recommended by the Council both for officers and members were announced by the Secretary.

The Auditing Committee (Drs. A. H. Smith and C. G. Stockton) reported that they had examined the Treasurer's accounts and vouchers and found them to be correct.

Dr. A. H. Smith read a paper entitled "Antitoxin Treatment of Pneumonia," which was discussed by Drs. Welch, Vaughan, Stockton, Thayer, and Smith.

Dr. Vaughan read a paper, written by himself and Dr. McClymonds, entitled "Bacteriology of Cheese," which was discussed by Drs. Ernst, Meltzer, F. C. Shattuck, Abbott, and Vaughan.

Dr. Thomson read a paper entitled "A Case of Chronic Infective Endocarditis with Streptococci found in the Blood before Death, Treated by Anti-streptococcus Serum, and Experimental Researches upon the Effects of Injections of Antitoxins upon the Kidneys," which was discussed by Drs: Tyson, Meltzer, Jacobi, F. C. Shattuck, Thayer, and Thomson.

Dr. Jacobi read a paper entitled "A Case of Septic Perforation of the Internal Carotid Artery; Autopsy Five Months after Death," which was discussed by Drs. Graham and Jacobi.

In the absence of Dr. Trudeau, Dr. Welch read the paper written by Drs. Trudeau and Baldwin, entitled "Studies of Antitoxins for Tuberculosis," which was not discussed.

Dr. Ernst read a paper entitled "The Effects of Freezing on Diphtheria Antitoxins," which was discussed by Drs. Vaughan and Ernst.

The following papers were read by title: "The Renal Form of Enteric Fever," by James C. Wilson. "A Chapter in Peripheral Pathology: the Circulation in the Feet," by Morris Longstreth. "Some Usually Overlooked Physical Signs in Chest Diseases," by Norman Bridge. "The Bacillus Subnormalis," by H. C. Ernst and A. A. Hopkins. "On the Significance of Jaundice in Typhoid Fever," by J. M. Da Costa. "Chronic Interstitial Nephritis," by I. N. Danforth. "The Diffuse Infiltrating Form of Secondary Melanosarcoma of the Liver," by L. Hektoen. "A New Pathogenic Pigment-producing Bacillus," by H. C. Ernst. "Neuralgia Paræsthetica," by J. H. Musser.

An amendment to the Constitution was introduced by Dr. Abbott, to the effect "That the Constitution shall be so amended that the election of officers and members shall take place on the second day of the meeting." Signed A. C. Abbott, V. C. Vaughan, F. Forchheimer, W. H. Thomson, W. T. Thayer, A. Jacobi.

On motion of Dr. Welch, it was resolved, "that a committee of three be appointed by the President to represent this Association in a National Conference in regard to forming a society for the diffusion of information concerning the knowledge and advantages derived from experiments upon animals.[1]

As the result of balloting, the following officers and members were elected:

[1] The President later appointed as such committee Drs. Welch, Pepper, and Janeway.

President.—G. Baumgarten.

Vice-President.—E. G. Janeway.

Recorder.—I. Minis Hays.

Secretary.—Henry Hun.

Treasurer.—W. W. Johnston.

Councillor.—James C. Wilson.

Representative on Executive Committee of Congress of American Physicians and Surgeons.—William Osler.

Alternate Representative.—Charles F. Folsom.

Honorary Member.—William M. Polk.

Members.—John W. Brannan, C. A. Herter, B. Sachs, F. A. Packard, J. K. Mitchell, S. Solis-Cohen, A. Stengel, H. F. Vickery, C. F. Withington, F. B. Mallory, F. Pfaff, J. N. Herrick, F. F. Wesbrook, A. D. Blackader.

On motion of Dr. Jacobi, it was *resolved*, that the thanks and congratulations of the Association be extended to President Shattuck for the success of this meeting.

It was further *resolved*, that the Secretary be instructed to convey the thanks of the Association to the Smithsonian Institution for the loan of the stereopticon, and to Mr. Roessle, of the Arlington Hotel, for the use of the room for the meeting.

The Association adjourned at 1.15 P.M.

HENRY HUN,
Secretary.

ABSTRACT OF REPORTS OF TREASURER 1887 TO 1898.

Year.	Subscriptions.	Sale of Transactions.	Interest.	Cost of Transactions.	Other expenses.	Balance in bank.
1887.	$ 580 00	. .	. .	$ 500 00	$ 22 80	$ 57 20
1888.	1533 20	. .	. .	956 01	115 32	519 07
1889.	694 00	$28 50	. .	831 61	224 98	184 98
1890.	1270 00	38 50	. .	922 01	77 49	493 98
1891.	1545 25	45 30	. .	529 43	140 80	1414 30
1892.	1200 00	. .	. .	646 84	125 11	1842 35
1893.	1395 00	47 70	. .	656 63	140 48	2487 94
1894.	899 83	64 30	. .	921 43	124 65	2405 99
1895.	945 00	40 80	$13 75	583 97	121 04	2700 53
1896.	1074 81	6 00	28 21	1265 52	164 85	1379 18
1897.	950 00	3 85	31 72	1205 43	142 68	1016 60
1898.	890 00	32 10	26 07	1074 53	123 08	767 16

NOTICE.

THE Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

THE PRESIDENT'S ADDRESS.

SOME REMARKS ON HOSPITAL ABUSE.

By FREDERICK C. SHATTUCK, M.D.,
of Boston.

Hospitals are so beneficent, and the lives of many of us are so bound up in them and their work, that we may at times fail to realize that they have any possibilities of evil, either as regards the public in general or our own profession.

With your permission I shall venture to lay before you a few thoughts which came into my mind on this question, some general subject pertaining to medicine seeming to be more suitable for the address with which it is my great privilege, thanks to your unmerited kindness to me, to open our session.

Though it is over four hundred years since this country was discovered, and more than two hundred and fifty years since real settlements by highly endowed members of the Anglo-Saxon race were effected, the first hospital was founded not much more than a century ago. Until approximately fifty years ago the population was relatively homogeneous, and even the largest cities were small enough for the inhabitants to know each other and each other's affairs. There were few poor, and neighborly succor efficiently met illness and the distresses which so often follow in its train. Then began the great Irish immigration, followed by that from almost every overstocked European country; the older cities grew apace, and new cities sprang up as the tide moved westward. The conditions of life changed with enormous rapidity, and every large city developed a class whose earnings or whose lack of thrift do not permit provision against the almost inevitable day when the bread-winner, afflicted with acute or chronic

disease, can win no bread, while the requirements of himself and his family can be but little, if at all, diminished.

We all know from personal experience how wonderfully helpful the members of this class are to each other in trouble of all kinds; also, that their helpfulness has clearly defined limits. The larger the class grows the more imperfectly are its members acquainted with one another and with one another's special needs; and much less are they, as individuals, known to the easier classes. Thus, organized and public must supplement private and individual help in time of need, and it is natural that the hospital should take a high, if not the first, place among the forms of help. We are all mortal; the vast majority of us are unsound somewhere; illness and disability come to many without any fault on their part. Health is an almost indispensable condition of support and usefulness. Its preservation, therefore, appeals directly alike to the head and heart of the community.

All the first hospitals in this country were founded by private individuals, public spirited, anxious to benefit their less fortunate fellow mortal and fellow citizens. But as cities grow large it is often found necessary for the taxpayers to aid and supplement private effort. We see, then, that the original cause for hospital foundation lay in charity—charity in its best and highest sense. Hospitals were designed to help those who could not help themselves; and it has been and is the pleasure as well as the duty of the medical profession to contribute its full share by rendering its services without direct pecuniary reward. But we should never forget that no physician can do conscientious work in a hospital without indirect reward, a portion of which is pretty sure to be pecuniary. The gain in knowledge, the stimulus to its acquirement, the development of the man and doctor alike, which the honest performance of hospital work surely brings, almost as surely lead to the better performance of private work, and hence to the demand for it. As hospital physicians, we are, I think, sometimes inclined to strike a false balance between the sacrifice of time and strength which hospital work demands and the return, which is none the less real because it is indirect and cannot be estimated with mathematical accuracy. Personally, I believe that this natural return is ordinarily ample, and that any conscious and deliberate attempt on our part to enhance it can only be lowering to ourselves and unfair to the general body of the profession.

And just as there are indirect advantages flowing to physicians from hospitals, so also do they flow indirectly to the rich who endow and maintain them, in that the rich profit by the skill acquired by the staff and by the advance in scientific knowledge secured by the minute study of collected cases of disease. Virtue may be its own, but it is not necessarily its only, reward.

I repeat that the primary purpose of hospitals is charitable; hence their immediate benefits should be reserved for the poor, for those who are unable to pay for medical attendance. Poor and rich are, of course, relative terms, and not easy of exact definition. A person may be able to pay one fee, perhaps several fees, but totally unable to pay for prolonged attendance. Medical attendance, moreover, stands on quite a different footing from almost every other necessary of life. There are different grades of food and clothing, even of fuel and light, between which, within certain limits, one can choose without detriment to health but with advantage to the pocket. The first cuts of meat are no more nutritious than the lower grades, and style alone may be the larger element in the cost of clothing, to say nothing of the choice of material. But the poorer a person is, the more purely dependent he and his are on his own exertions, the more important is it for him to have the best medical care attainable. Here economy may be the wildest extravagance. This is an aspect of hospital abuse which cannot be lost sight of. There is no clearly discernible line of cleavage, and, therefore, abstract justice cannot be done in every case; as in most other branches of human activity, substantial justice is the best we can hope at present, at least, to attain. Medical charity in hospitals and dispensaries should be freely extended to those who require it, denied to those who do not and from ignorance or parsimony demand it. The community suffers if provision is insufficient or proper access is difficult. The community also suffers if no questions are asked, the independence and self-respect of the laity being undermined, and the medical profession failing to receive returns which justly belong to it. Alike as citizens and professional men, we should carefully scrutinize the claims of every new charitable medical institution, and refuse our aid and countenance unless satisfied that it is likely to meet a real need in the community.

The same care should be exercised with regard to abuse creeping into existing institutions. The matter lies really in the hands of our

profession. If no physician would serve or aid in promoting a medical charity, so-called, founded mainly on sentimental or selfish considerations, such would soon cease to exist, and the millennium would be at hand. There is too much reason to believe that hospitals and dispensaries are sometimes started purely in the selfish interest of members of our profession.

The second great function of hospitals—second in point of time evolution, though not, I believe, in point of importance—is the educational function, the advancement and dissemination of knowledge. On this function I need not dilate to this audience. It is, of course, more obvious to us than to the laity; but their attention is being more and more called to it. They are quick to see the truth and to recognize the powerful stimulus to the staff to do first-class work afforded by the critical eyes of bright students. The clinical teacher must study his cases carefully; compulsion acts more imperatively on him than on the hospital physician who is not also a clinical teacher. The necessities of teaching and the demand for much material from which to select has been used as an excuse for the abuse of hospitals and dispensaries, and to a certain extent such excuse may be valid. Students should become familiar with as wide a range of disease as possible. The didactic lecture in medicine and surgery is slowly but surely falling into the background, teaching becoming more and more clinical. Patients may be made to pay in their persons if not from their pockets. The student and clinical teacher demand material; the practitioner wants patients. When the student becomes a practitioner his point of view changes. But he should not forget that he, when a student, probably gained in remunerative knowledge more than the equivalent of a few cases which, after he has gone into practice, seek advice at a hospital instead of paying his fees. Our direct losses loom up larger than our indirect gains. I do not mean to imply that a teaching hospital is free from responsibility in regard to this matter. I merely want to indicate that there are two sides to this question, at the same time stating my conviction that very little injustice need be done if a due sense of responsibility is felt and influences action.

Complaint in the medical press of hospital out-patient departments and dispensaries seems to be endemic in England, and there has been of late an epidemic in this country; legislation on the subject has even been seriously considered. It is claimed that the doors of these

institutions are thrown open so widely as to entail great hardship on many worthy members of the profession. That there is some ground for these complaints I fear there can be no question. For some eight years I did out-patient work in the Massachusetts General Hospital, and have no reason to believe that the conditions are materially different now from what they were at that time. The number of cases of deliberate intention to avoid payment for advice was, as I remember, small. Some residents of the city, apparently able to pay, came, seemingly without wrong intent, to get an opinion and see how far it coincided with that of their doctors. More came thus from the country, under the impression that the city must contain more wisdom, not knowing whom there to consult, and not having told their regular advisers that they wanted further advice. The reputation of the hospital, and sometimes the idea derived from the name—"Massachusetts General"—that it is a State institution, to the benefits of which as taxpayers they had a right, determined their coming. Not infrequently patients would come, more commonly from out of town, either with their physician or with a letter from him, asking for a consultation, and perhaps a detailed opinion in writing—no light demand, considering the number of patients requiring attention.

For some years now at the Massachusetts General Hospital a paid medical officer questions applicants to the out-patient department as to their circumstances, and refuses entrance to those who do not seem to him proper cases for free advice. It is also his duty to exclude such diseases as measles, scarlet fever, and the like from the waiting-rooms, in order that their spread may be limited. This is a plan which does not involve a hospital in great expense—five hundred dollars per annum at the Massachusetts General Hospital, with an average of about one hundred new patients a day—as the services do not require more than a couple of hours a day, seems to me as efficient as any plan which has been suggested, and one which it is not unreasonable to expect all similar institutions to carry out.

There is another ground for complaint against hospitals about which less has been said. I refer to the growing practice of attaching paywards to hospitals, which, let me repeat once more, are founded and exist for charitable and educational purposes. Patients who pay from twenty to fifty dollars per week for private rooms ordinarily serve neither of the above purposes, and provision for them here seems to

me unfair and improper unless to a very limited extent. This is not a legitimate mode of providing revenue for the care of the sick poor. Our well-to-do citizens are amply able, and I am convinced more than willing, to provide for such cases through gifts, bequests, and taxes. The chances are strong that a hospital that cannot be maintained without the resort to this practice is in whole or in part unnecessary to the community in general, and should, consequently, in whole or in part, close its doors until the community in which it is situated grows up to it. One great and well-known hospital derived fifty-five thousand dollars from this source last year. I am told that other great hospitals are making large investments in this field. I am perfectly well aware of the fact that strangers in the city fall ill in hotels, and that residents are for one reason or another sometimes so situated at their abodes that proper care is difficult or impossible to secure. I know what a boon it sometimes is to patient and physician alike to have access to a well-organized hospital. But this need not and should not be a charitable hospital. This class of patients is sufficiently large in every considerable city to maintain one or more hospitals or infirmaries: private in that they are designed for private patients, public in that any physician can send his patient thither and assume personal care of him, making such professional charges as his wisdom and conscience dictate. This is free-trade in medicine. In a large hospital it is, from an administrative point of view, impossible to allow physicians other than members of the staff to care for patients within its walls. The small private hospital or infirmary can be made to yield a good return on the investment, and no injustice is done to anybody. And it seems to me that injustice to somebody is inevitable when well-to-do patients are admitted to hospitals designed for the sick poor. If the staff is allowed to receive fees for attendance on such patients its members are given an unfair advantage over those members of the profession without hospital appointments, and the hospital becomes a sort of medical trust. The indirect benefits of hospital service are quite sufficient. If the members of the staff are not allowed to take fees the well-to-do patient is injured by receiving gratis services for which he is able to pay and should pay; the time and skill of the attendant is diverted from the sick poor or from such use as he might wish to make of them, and the sum of professional earnings, now none too large, is unfairly diminished. Commercialism tends to

degrade the medical profession, and if well-to-do patients are to be cared for in our great hospitals, it seems to me that the evils of free are less than those of paid professional service.

The Massachusetts General Hospital has eight private rooms of the class I now allude to. Years ago the staff itself established the rule that no fees should be received for attendance on inmates of the hospital, and a printed notice to that effect is placed in each of the private rooms.

The hospital physician can keep his private hospital if he will, or he can, just like any other physician in the town, send his patients to an infirmary. The charitable and educational institution should not step in to save its staff the trouble of housekeeping and of providing and superintending nursing for patients in easy circumstances. It should not demand of its staff unrequited service save for the sick poor. It should not place any unnecessary obstacles in the way of full and free competition between members of our profession. To the exaction of the payment of a few dollars a week from patients who can afford it, who are treated in the ordinary wards, and who can be used for teaching, if suitable cases, I can see no valid objection. The self-respect of the patient is maintained by rendering some return for much needed care, which his circumstances preclude his securing at home, and no just ground for complaint is afforded practising physicians unattached to hospitals.

In this whole question we have a responsibility which we cannot escape. The more fortunate a man is the more mindful should he be of the rights of others, especially of his professional brethren. The staff of the hospital or dispensary should co-operate fully with the trustees, giving them the full benefit of their more intimate knowledge of all professional matters, and always remember the broad therapeutic principle—"*ne quid noceat.*"

THE SIGNIFICANCE OF ALBUMOSURIA IN MEDICAL PRACTICE; SUGGESTED BY A FATAL CASE OF ALBUMOSURIC MYXŒDEMA TREATED WITH THYROID EXTRACT.

By REGINALD H. FITZ, MD.,
OF BOSTON.

THE following case of myxœdema is reported more particularly for the purpose of calling especial attention to the presence of a symptom which, with but a single exception so far as I am aware, has hitherto been unrecorded in this disease except as a mere statement of fact in the *Practice of Medicine*, by Wood and Fitz. The patient therein referred to was seen by me in consultation with Dr. M. L. Chamberlain, of Boston, to whom I am indebted for permission to give the following account and for information concerning the progress of the malady.

The case is of further interest, if not importance, in showing that the prognosis of myxœdema still may be grave, despite the immediate and repeated benefit so generally resulting from the use of thyroid preparations.

I first saw Mrs. ——, November 17, 1895. She was fifty-three years of age, and had lived the greater part of her life in Vermont. The last two years had been spent in California. She had never been pregnant. As a girl she suffered considerably from discomfort referred to the stomach, in the region of which there would be a sense of distention for a day or two at a time. Cramps would occur suddenly, and tenderness along the spine was complained of. With these exceptions she enjoyed good health throughout the greater part of her life, recalling to mind solely an operation for anal fistula when she was about forty-seven years old.

At the age of forty-nine, while in Vermont, she observed a gradual loss of flesh, strength, and color. A year later, when tired, would feel a griping sensation in the back of the neck and a pain between the shoulders. These discomforts were noticeable especially on going down hill. There was also a

temporary stiffness of the joints in the morning. At this time the eyelids were slightly swollen, and an increased flow of saliva began, a symptom which has continued since, and persists at present.

In the following year (1893), while in California, the joints again became appreciably stiff, and she felt a sense of numbness in the right heel, in the knees immediately above and below the joint, and in the fingers of the right hand. In 1894 the stiffness diminished somewhat, but the numbness persisted. In the fall of this year the teeth were troublesome, and, despite the care of a dentist, became painful, and since have remained in this state. An upper canine tooth is said to have extended into the bone one-fourth of an inch. There was a metallic taste in the mouth, and she became unable to masticate resistant food, being obliged to live upon soft articles of diet. Walking now caused so much fatigue that she was obliged to give up active exercise. The griping at the back of the neck and the pain between the shoulders continued to be annoying at times, and she suffered also from wakefulness.

In January, 1895, superficial swellings first were noticed. They appeared as an enlargement of the back of the neck, a lump beneath the jaw, hypertrophy of the tongue, and later indurations in the legs and arms. At first the swellings would vary temporarily in size, and that in the neck would lessen somewhat under the influence of fomentations, but later the enlargement remained constant. The voice now was changed, and the increased flow of saliva became a more or less constant drooling. In the course of a few months, in consequence of a loose molar tooth, the jaws were prevented from closing. The tooth was extracted, but the jaw and the neighboring portion of the tongue became sore and, finally, a fragment of dead bone was removed.

At the time of my first visit Mrs. —— walked with difficulty on account of muscular stiffness and a sense of tightness of the skin. There was no evidence of mental impairment, nor had such been observed by her friends. Her face was pale, moderately swollen, and expressionless from partial effacement of wrinkles and furrows. In sharp contrast was the elevation of the eyebrows and wrinkling of the forehead from apparent tension of the occipito-frontalis muscle. The upper eyelids were relatively normal, but the lower lids were somewhat puffy. The lips were slightly thickened and everted, the surface roughened. Especially conspicuous was the greatly enlarged and resistant tongue filling the partially opened mouth. The dorsum of the tongue was dry, although the flow of saliva was constant. The submaxillary region was prominent, presenting the appearance of a double chin, and both submaxillary salivary glands were greatly swollen and dense. The back of the neck was smooth and much swollen, like that of a very obese person, but was dense and resistant to the touch. The neck measured from 16½ to 17½ inches in circumference. The hands and feet were cold. The skin covering the back of the hands was thickened, coarsely wrinkled, the surface being rough and of a dirty yellowish tint, the whole appearance suggesting that of a fowl's claw. The skin covering the front of the chest and abdomen was normal,

but that of the forearms, legs, feet, back, and buttock was pale, dry, smooth, tightly drawn, not displaceable from the subjacent structure in consequence of the resistance of the subcutaneous tissue. The anterior wall of the vagina was smooth, thickened, and dense like the abnormal portions of the skin. There were no supraclavicular swellings. The hair was coarse and dry, but the nails were normal in appearance. The thyroid gland was not palpable. Nothing abnormal was found on auscultation and percussion of the chest and on palpation of the abdomen. The temperature was 98 4° F.

The examination of the blood by Dr. R. C. Cabot showed 5,030,000 red corpuscles, 11,600 leukocytes, and 33 per cent. of hæmoglobin. The differential count gave 74 per cent. of polynuclear leukocytes and 23 per cent. of lymphocytes.

On the addition of nitric acid to the urine a dense, white precipitate was formed, occupying nearly one-half the volume of urine. The precipitate was dissolved when the specimen was boiled, but reappeared on cooling. When the urine in a test-tube was boiled it became opaque until the boiling-point was reached. It then became clear, and thus remained until the liquid was cool, when a white precipitate formed. Under the microscope a few red blood-corpuscles and an occasional hyaline and granular cast were seen.

The dissolving of the nitric acid precipitate by heat and the formation of a white precipitate when the boiled urine was cooled led me to suspect the presence of albumose, and Prof. E. S. Wood was asked to test further for this substance. He informed me that after boiling and filtering the urine to free it from albumin, the clear filtrate when acidulated with acetic acid and heated gently became opaque, but the opacity disappeared on boiling, and a white precipitate formed when the fluid was cooled. Acetic acid and ferrocyanide of potassium gave a precipitate which dissolved when the mixture was boiled, and reappeared as the temperature fell. The biuret reaction was positive.

Prof. Wood analyzed the urine from this patient repeatedly during a period of six weeks. A trace of albumin was present usually, but albumose was found constantly, by estimate varying from $\frac{1}{8}$ per cent. to $\frac{1}{4}$ per cent. December 10, 1895, a quantitative determination was made and showed 0.93 per cent. of albumose. The percentage of urea on this day was 3.63 and the total quantity 18 66 grammes.

The diagnosis of myxœdema was made and the treatment with thyroid extract begun, the five-grain tabloids of Burroughs, Wellcome & Co. being used. The dose of five grains on the first day was increased by one tabloid daily, but on the third day there was a sense of precordial oppression and the pulse became quickened. The dose then was diminished to one or two tabloids daily for a week, when it again was raised to three five-grain tabloids in each twenty-four hours.

I saw Mrs. —— a second time on December 10, 1895, a little more than three weeks after my first visit. The change in her appearance had greatly improved, although previous to the use of the thyroid extract her condition

was steadily deteriorating. At the end of the first week of thyroid treatment the œdema suddenly left the eyelids, but a watery œdema, pitting on pressure, appeared and persisted in the feet. The flow of saliva diminished, the swollen tongue became smaller, and the pain in the shoulders was less disturbing. In the third week of treatment the swelling of the neck and of the submaxillary glands was noticeably lessened and the expression of the face became more mobile. The weight at the beginning of the thyroid treatment was 125½ pounds, and there had been a loss of about three pounds each week. The quantity of urea eliminated increased from 11 to 16 grammes. The appetite was unaffected, but the pallor and debility were greater than when first seen. The pulse varied between 83 and 107 beats per minute, and the temperature remained in the vicinity of 99.7° F.

It was considered desirable to continue the use of the thyroid extract under careful supervision, that cardiac weakness might not prove a source of danger. The especial discomforts produced by it were fleeting pains in the muscles or in one joint or another, precordial constriction, and a choking sensation—all more likely to occur at night, when the greatest quantity of the thyroid preparation had been taken within a limited number of hours.

Preparations of iron, arsenic, manganese, strychnine, digitalis, and nitroglycerine were given from time to time as the indications for their use were apparent. On account of the progressive weakness of the patient, despite the early improvement in the surface manifestations, the thyroid preparation was discontinued from time to time.

At a third visit, February 25, 1896, Dr. C. F. Folsom also saw the patient. At this time, although the expression was brighter, she was pale, weak, and emaciated. The especial improvement was in the condition of the skin, which was smooth, moist, and free from the yellow discoloration so marked at the outset. The hands were warm, the hair was moist and less bristling, but the brawny induration of the back of the neck and the swelling of the tongue and submaxillary glands had not materially diminished in the previous two months. It was decided to continue the use of the thyroid, and from seven to nine grains were given daily for a week, during which time the pulse was about 100 and the temperature varied from 99.2° to 100.4° F. A sudden severe attack of precordial pain then occurred, and the use of the thyroid was discontinued for four weeks. During this time the pulse fell to the normal and became stronger, the salivation lessened, the weight slightly increased, but the tongue felt as if it was enlarged somewhat. The thyroid extract then was given in one-grain doses, and for greater convenience in supervision and care, Mrs. ——— entered the Boston City Hospital, where she remained under the charge of Dr. Folsom, to whom I am indebted for the report of her further progress.

She was admitted to the hospital April 18, 1896. The circumference of the neck then was fifteen inches, the tongue was about four inches wide and one inch thick. The head could not be bent backward, nor could the chest be touched with the chin. The hands and feet were cold, the skin was smooth

and the hair moist. The blood examination showed 84 per cent. hæmoglobin, 4,532,000 red corpuscles, and 10,500 leukocytes. The patient received one grain of thyroid extract daily, but she gradually became weaker, took but little nourishment, decidedly failed on the 26th of April, and died early on the following day. There was no autopsy.

There having been some difference of opinion among the physicians who saw this patient as to the exact nature of the disease, the reasons for the diagnosis of myxœdema may be summarized. There were present "the firm swelling of the skin, not pitting on pressure, inelastic, adherent to the parts beneath, and not affected by gravitation; the dryness and roughness of the skin, tending, with the swelling, to obliterate all lines of expression; the imperfect nutrition of the hairs, . . . the local tumefaction of the skin and subcutaneous tissue noticed in various parts of the body, . . . an affection of the teeth homologous with that of the hairs, just mentioned; the remarkable physiognomy; the slow . . . monotonous voice . . . and elimination or apparent absence of the thyroid gland." These are among the characteristics of myxœdema described in the Report of the Committee of the Clinical Society of London (1888, vol. xxi., Supplement, p. 178). The mental impairment and subnormal temperature alone are lacking to complete the picture. But mental disturbances were absent in 27 out of 46 cases tabulated by the committee (*op. cit.*, p. 14). The temperature was normal in 8 cases, and in a few was 99° F., or even higher, though never above 100° F. The swelling in the back of the neck was duplicated in Dr. Ord's case, No. 87, in which there was a "swelling at back of neck over trapezius so that he cannot bear to wear a collar." Salivation was present in 3 of the committee's cases, and the submaxillary gland of Hale White's case (*op. cit.*, p. 41) showed marked changes. A large, swollen tongue was noted in 52 cases.

If the correspondence in clinical characteristics is not considered as sufficient for the confirmation of the diagnosis, additional evidence is furnished by the effects of the treatment with the thyroid extract. According to Murray (*Twentieth Century Practice*, 1895, iv. 712), these are rise in temperature, disappearance of swelling, loss of weight, a soft, smooth, moist condition of the skin, growth of the hair, improvement in the mental condition, and increase in the elimination of urea. Her temperature became somewhat higher, and the previously

cold hands were warm. The swelling diminished, there was a loss of weight, the skin became soft, smooth, and moist, and the elimination of urea increased. A growth of hair was not conspicuous, since there was no tendency to alopecia; but a considerable improvement in its nutrition was apparent from the return of its normal characteristics.

The failure of the thyroid treatment to accomplish more marked relief is in striking contrast to the almost constant benefit derived from its use in the treatment of myxœdema. Mitchell Clarke (*Brit. Med. Journ.*, 1892, ii. 451), however, reports two cases in which thyroid treatment proved unsuccessful, and Macpherson (*Edinb. Med. Journ.*, 1892, xxxvii. 1021), although causing improvement by thyroid grafting, did not remove the myxœdematous condition. Byron Bramwell (*Edinb. Hosp. Rep.*, 1885, iii. 116) gives an account of two fatal cases of myxœdema during or shortly after thyroid treatment; in each instance the death was sudden.

I am indebted to my colleague, Dr. E. G. Cutler, for the following summary of a case under his charge.

"A patient in whom I made the clinical diagnosis of myxœdema had gradually, over a period of a year and a half, come into the following condition: The skin of the face, neck, shoulders, hands, arms, legs, feet, was pale and a little glossy, rather dry, much distended by a subcutaneous growth which did not pit, and apparently was not fat. The wrinkles in the face were obliterated, the hair on the head had become sparse and dry, the hands and feet were much wrinkled and the skin and nails coarse and rough. Speech was slow and peculiar. The mental condition was variable; at times the patient was rather inclined to be talkative, but the range of subjects was limited; at other times the patient would be quiet for hours and rather somnolent. Frequently there was mild delirium at night, with occasional hallucinations of sight. The patellar reflex was absent. The pulse was slow, the surface cool, and the temperature in the mouth 98° F., though no complaint of cold was made. The urine was free from albumin. The thyroid could not be made out. Toward the end there was marked tendency to somnolence. Thyroid tablets, five grains each, were given up to nine a day, for two months, beginning with small doses, but with little effect. Death was sudden and apparently due to syncope."

The novel feature of my case was the albumosuria, which continued throughout the progress of the disease from the time it was first observed. Occasional or slight traces of albumin were noticed in 20 out of 90 cases, and in 1 a large quantity, in the series tabulated by the London Clinical Society's Committee (*op. cit.*, 21), in which men-

tion was made of this condition, and in 21 out of 112 cases collected by Hun and Prudden (*Amer. Journ. Med. Sci.*, 1888, xcvi. 1). Murray (*loc. cit.*, 722) states that "mucin" has not been found in the urine of human myxœdema, but refers (*loc. cit.*, 726) to Halliburton's discovery of an abundance of "mucin" in the urine of a sheep that developed myxœdema two years after the thyroid was removed by Horsley. Buzdyan (*Wien. klin. Wochenschr.*, 1891, iv. 510), however, found traces of "mucin," but no albumin, in the urine of a patient examined by him. The only instance of myxœdema in which I have found mention of the occurrence of albumosuria is the patient of von Jaksch (*Prag. med. Wochenschr.*, 1892, xvii. 602). The case was one of typical Basedow's disease, in which there were present a swelling of the legs, regarded as myxœdematous, and an albumosuria observed during a period of six months.

As is well known, this term is applied to the presence in the urine of a peculiar substance first observed by Bence Jones (*Philosoph. Trans. Roy. Soc. Lond.*, 1848, Pt. 1, p. 55) in 1845. As described by him: "It gave no precipitate with an excess of nitric acid unless left to stand, or unless heated and left to cool, when it became solid. This solid redissolved by heat, and again formed on cooling. Continued boiling with strong nitric acid evolved but little gas, and did not quickly hinder this reaction. Hydrochloric acid gave the same solid precipitate, soluble by heat. Strong acetic acid gave only a slight precipitate, which redissolved by heat. Caustic potash and sulphate of copper gave a splendid bright-blue, clear liquid, passing over when heated to a claret color, . . . coagulated firmly with heat, very perfectly with a drop or two of acetic acid."

According to Maly (*Herrman's Handb. d. Physiol.*, 1881, v. 2, 94), the product of the gastric digestion of albuminous substances was designated albuminose by Mialhe, in 1846, but subsequently Lehmann named it peptone. Meissner and his pupils, in a series of articles published between 1847 and 1853, assumed the existence of a number of products of digestion, intermediate between albumin and peptone, to which the terms parapeptone, metapeptone, dyspeptone, α, β, and γ peptone were applied. In 1869 Kühne received from Stokvis a specimen of urine which presented reactions similar to those observed by Bence Jones, and Kühne regarded the substances as identical. In the same year Gerhardt (*Deutsches Arch. f. klin. Med.*, 1869, v. 212)

sought in the urine for other albuminous substances than serum albumin, and discovered a variety, called by him "latent," which resembled in its characteristics one of the peptones described by Meissner. He found it in a number of diseases, and observed that it was to be met with in persons whose temperature, frequently or constantly, was in the vicinity of 104° F. Senator (*Arch. f. path. Anat.*, etc., 1874, lx. 476), later, observed in the urine easily distinguishable quantities of what he regarded as peptone. He recognized that this substance might have been produced in albuminous urine by the process of boiling used in its isolation, but suggested that it may have been present in the freshly voided urine. In support of this view he referred to Gerhardt's discovery of a substance resembling peptone in the urine in which no evidence of ordinary albumin was to be obtained. Leick (*Deutsche med. Wochenschr.*, 1896, xxii. 22), however, states that although boiling may produce albumose from albumin such a result does not necessarily follow, since numerous specimens of albuminous urine were so treated without the formation of albumose. Even in experiments on isolated albumin the quantity so transformed was too small to be significant. It was recognized also by Senator as possible for the albumin of albuminous urine on its passage from the kidneys to the bladder, and during its retention in this viscus, in part to be converted into peptone, in accordance with the statement of Eichwald, that fluid albumin in contact with animal tissues at the temperature of the body is readily transformed into peptone. Eichwald found this substance in the urine of nephritis, and Obermüller, in 1873, in that of scarlet fever and Asiatic cholera. Gowers (*Lancet*, 1878, ii. 3), a few years later, noticed its presence in a patient who previously had suffered from glycosuria.

About this time Kühne gave the term hemialbumose to the substance in question, which was considered to correspond with the γ peptone of Meissner, and Schmidt-Mülheim (*Arch. f. Physiol.*, 1880, 33), designated it propeptone. Its properties were studied also by Salkowski (*Arch. f. Path.*, etc., 1880, lxxxi. 552). All these observers recognized the resemblance between this so-called peptone, hemialbumose or propeptone, and the substance discovered by Bence Jones. The methods employed for the recognition of the "peptone" were faulty, especially from the difficulty of wholly removing the albumin often associated, and from the frequent, if not constant, presence of "mucin,"

which also was precipitated by the alcohol used in isolating the substance, and which gave rise to reactions similar to those attributed to the peptone. Hofmeister (*Ztschr. f. physiol. Chem.*, 1880. iv. 253) consequently devised a method for the isolation of the so-called peptone which should free it from these sources of error. This method, and the improvement subsequently made by Salkowski, served as the basis of numerous contributions to the study of what has been designated as "peptonuria" since that time.

The researches of Kühne and of Kühne and Chittenden (*Ztschr. f. Biol.*, 1883, xix. 159, 219; 1884, xx. ii) led to the use of the term albumosuria as a substitute for propeptonuria. According to these investigators, albumose, hemialbumose or propeptone was a mixture of four albumoses which were designated protalbumose, deuteroalbumose, heteroalbumose, and dysalbumose. Each varied slightly from the other, especially with reference to the degree of solubility in water and in behavior toward solutions of sodium chloride, being either soluble or insoluble in dilute solutions, and precipitated by concentrated solutions or in the presence of an acid according to the variety of albumose concerned. When in solution they were not precipitated by heat alone, but if precipitated by acids or salts were redissolved at a boiling temperature, and were precipitated when the solution was cooled. According to Huppert, Matthes, and Rosin, they become opaque at temperatures of 150° to 152° F., and clot at 166° to 178° F. They were precipitated by nitric acid and by acetic acid, by magnesium sulphate, concentrated solutions of sodium chloride, and of ammonium sulphate in an acid, alkaline or neutral solution, and gave the biuret reaction.

Like albumin, they were precipitated by nitric acid, ferrocyanide of potassium and acetic acid, sodium chloride and acetic acid, and ammonium sulphate, but they were not coagulated on boiling. They resembled peptones in being soluble at a boiling temperature, precipitating as the fluid became cool, and in giving the biuret reaction. They differed from peptone according to Kühne (see article by Wenz, *Ztschr. f. Biol.*, 1886, xxii. 1) in being thrown down by ammonium sulphate.

The search for albumose then became instituted, and the term albumosuria soon replaced that of propeptonuria, although for a long time it was considered to be a different condition from peptonuria.

The distinction made between albumoses and peptones, based upon the insolubility of the former in ammonium sulphate, was opposed by the observation of Neumeister (*Ztschr. f. Biol.*, 1888, xxiv. 267) that this agent does not precipitate entirely all the albumoses, especially deuteroalbumose. Stadelmann, in 1894, concluded that peptone, as distinguished from albumose, never occurred in fresh urine, although it might be found in stale albuminous urine from the action of bacteria upon the albumin. Von Noorden and Senator (*Deutsche med. Wochenschr.*, 1895, xxi. 217) accepted this view and maintained that both peptonuria and propeptonuria were albumosuria. According to Senator, if a part of the urine which gives a positive reaction to Salkowski's test, and therefore is considered to contain peptone, is slightly acidified and treated with ammonium sulphate in excess and filtered, there will be no biuret reaction in the filtrate, indicating the absence of Kühne's peptone, which should be soluble in the ammonium sulphate.

Albumose was found not only in the gastric contents during the digestion of albumin, but also in artificial peptone-preparations, and by Fleischer (*Arch. f. path. Anat.*, 1880, etc., lxxx. 482) in normal bone-marrow. The discovery of its presence in semen is generally attributed to Posner (*Berl. klin. Wochenschr.*, 1888, xxv. 417), but this observer and others who have written upon the subject, with the exception of Kahler (*Prag. med. Wochenschr.*, 1889, xiv. 33) have overlooked the fact that Bence Jones (*loc. cit.*), the discoverer of albumose, found it not only in the urine and in pus, but also "in the secretion from the vesiculæ seminales." Virchow (*Arch. f. path. Anat.*, etc., 1852, iv. 309) recognized in the bone-marrow of osteomalacia a substance which he considered to resemble that described by Bence Jones. Salkowski (*Arch. f. path. Anat.*, etc., 1880, lxxxi. 166; 1882, lxxxviii. 394) sought successfully for it in the liver and spleen of leukæmia and in the liver of acute yellow atrophy. Miura (*Arch. f. path. Anat.*, etc., 1885, ci. 316) observed it in the liver, heart, and kidneys of phosphorus poisoning produced experimentally, and in the organs of a case of puerperal fever. Schültzen and Riess (*Ann. d. Char-krankenh.*, . . . zu Berlin, 1869, xv. 1) previously had found albumose in the urine of phosphorus poisoning. Fischel (*Arch. f. Gynäkol.*, 1884, xxiv. 400) stated that albumosuria was present almost constantly during the involution of the puerperal uterus, and Köttnitz (*Deutsche med. Wochenschr.*, 1888, xiv. 613) when there was a macerated fœtus.

Albumosuria has been produced experimentally by Lassar (*Arch. f. path. Anat.*, etc., 1879, lxxvii. 157) by rubbing petroleum into the skin of animals. Plosz and Gyergai (*Arch. f. d. ges. Physiol.*, 1875, x. 53), and Hofmeister (*Ztschr. f. physiol. Chem.*, 1881, v. 127) caused it by the injection of peptone into the veins, and Jitta (*Jahresb. u. d. Fortschr d. Thier Chem.*, 1885, xv. 474) by the subcutaneous injection of glycerin. Rosenheim (*Allg. med. Centrz.*, 1897, lxvi, 1132), states that he has seen albumosuria follow the ingestion of large quantities of albumose in a case of severe intestinal disturbance.

The clinical importance of albumosuria has been made a matter of study by many observers whose results in the main agree. Although published under the titles of peptonuria, propeptonuria, or albumosuria, the method used for the purpose of determining the presence of the albumose was that of Hofmeister, or, in more recent years, by this method as modified by Salkowski (*Centralbl. f. d. med. Wissensch.*, 1894, xxii. 113). The chief advantages of the modification are gain in time and the use of a much smaller quantity of urine.

The urine to be tested must first be freed from any albumin present by acidifying from 20 to 50 c.c. with acetic acid, adding an equal quantity of saturated solution of common salt, boiling and filtering. The albumins and albumoses are precipitated, but the latter are redissolved at the boiling temperature. The filtered fluid containing the albumose in solution is to be placed with a few drops of hydrochloric acid in a beaker, and then a solution of phosphotungstic acid is to be added while precipitation continues. The precipitate is to be consolidated by gentle heat into a coherent or powdery substance. The supernatant fluid is to be poured off and the precipitate washed with water, is to be dissolved in a solution of soda (sp. gr. 1.16), which is to be added drop by drop until a blue or colorless solution results. The solution, if blue, is to be decolorized by heat, and a few drops of a 1 per cent. solution of sulphate of copper are to be added to the soda solution, when a red or violet color, the biuret reaction, results if albumose is present.

Recently Salkowski (*Berl. klin. Wochenschr.*, 1897, xxxiv. 353) has called attention to a possible source of error. He has found that urobilin, which is precipitated by phosphotungstic acid, gives also the biuret reaction, and that, consequently, a specimen of urine tested by the Salkowski method may give a positive result, but due to urobilin,

and not to albumose. Urobilin in the urine does not necessarily produce this reaction, but is more likely to in case the spectroscopic examination of the urine gives a well-marked urobilin line. Leick (*loc. cit.*) had already suggested a modification of the Salkowski test, having found it necessary to use a stronger soda solution or a larger quantity of the weaker variety. After removing the albumins he added also the neutral lead acetate to the filtrate for the purpose of precipitating "mucin," coloring matter, and any remaining albumin. According to Salkowski, albumose also is precipitated by this reagent, and the negative results of the examination by this method could not exclude the possibility of albumosuria. Fortunately, for practical purposes, the question relates to quantity and not to mere presence. Bang (*Deutsche med. Wochenschr.*, 1898, xxiv. 17) also has devised a method for finding albumose in the urine, even in a dilution of 1 : 4-5000, when urobilin is present in any considerable quantity. A test-tube containing 8 grammes of finely powdered ammonium sulphate to 10 c.c. of urine is to be heated till the former is dissolved. The contents are to be boiled for a minute, centrifuged for another minute, and the clear liquid poured off. The residue, containing albumose, albumin, urobilin, uric acid, and urates is to be stirred in alcohol (97 per cent.), which dissolves the urobilin, and is to be poured off. This residue is boiled with a little water and filtered; the filtrate gives the biuret reaction if albumose is present. The centrifuge may be dispensed with if the quantity of albumose is considerable, and the following method employed. After boiling some of the albumose adheres to the wall of the tube. The liquid is to be poured out and the adherent residue washed with alcohol, to which a little chloroform is to be added if there is presumably much urobilin. The biuret test is to be applied to the filtrate from the residue dissolved in water. The presence of urobilin in the alcoholic extract is shown by a fluorescence when a few drops of a solution of zinc chloride are added. Hæmatoporphyrin may simulate albumose by causing a red color when the alkali of the biuret test is used. Its presence is to be suspected if the alcoholic extract is red and proven by the spectroscope. If, therefore, the alcoholic extract is red the urine should first be treated with barium chloride, which precipitates hæmatoporphyrin.

Maixner (*Vrtljschr. f. d. prakt. Heilk.*, Prag., 1879, cxliv., 75; *Zeitschr. f. klin. Med.*, 1884, viii. 234), Von Jaksch (*ibid.*, 1883,

vi., 413), and Pacanowski (*ibid.*, 1885, ix. 429) examined hundreds of cases of various diseases by Hofmeister's method and came practically to the same conclusion, that albumosuria was oftenest found in suppurative processes associated with the retention and disintegration of pus, in acute infectious diseases and in affections associated with more or less extensive destruction of tissues. (Köppen (*Arch. f. Psychiat*, 1888–89, xx. 825) observed it in a number of insane persons, especially those who were maniacal or delirious. W. Robitschek (*Zeitschr., f. klin. Med.*, 1894, xxiv. 556), Senator (*Deutsche med. Wochenschr.*, 1895, xxi. 217), and Leick (*loc. cit.*), using Salkowski's method, arrived at a similar result. The albumosuria was relatively constant in deep-seated suppuration and in acute fibrinous pneumonia, especially during resolution.

Gerhardt's claim that ordinary or "latent" albuminuria occurred in persistent or frequent elevations of temperature above 104° F., and the statement of Krehl and Matthes (*Deutsches Arch. f. klin. Med.*, 1895, liv. 501) that albumosuria was almost constant in fever, are subject to a different interpretation in the light of Salkowski's discovery concerning the reaction of urobilin.

Albumosuria has been found in various chronic affections as well as in those of an acute nature. Among these, chief importance is to be attached to the albumosuria of osteomalacia or of affections regarded as of this nature.

Such cases have been reported by Bence Jones (*loc. cit.*), Kühne (*loc. cit.*), Kahler, (*Prag. med. Wochenschr.*, 1889, xiv. 35), Stokvis and Ribbink, Matthes (*Verhand. d. Cong. f. Innere Med.*, 1896, xiv. 476), Huppert (*Zeitschr. f. physiol. Chem.*, 1896–97, xxii. 500), and Rosin (*Berl. klin. Wochenschr.*, 1897, xxxiv. 48). According to Kahler these are not examples of true osteomalacia, but of myelogenous tumors, sarcoma, lymphoma, myeloma, especially of the bones of the thorax. Matthes (*loc. cit.*) in four cases of osteomalacia, which probably were of multiple myeloma, isolated from the urine a substance with the characteristics of albumose, but which, when digested for some time, gave rise to a ferrated nuclein. Hence the substance was regarded by him as a nucleo-albumose, arising from the ferrated nucleo-albumin of bone-marrow, discovered by Nasse. It was not found in typical puerperal osteomalacia.

Raschkes (*Prag. med. Wochenschr.*, 1894, xix. 649), on the con-

trary, states that albumosuria occurs in senile osteomalacia, and Hammer (*Arch. f. path. Anat.*, etc., 1894, cxxxvii. 280) and Marckwald (*Arch. f. path. Anat.*, etc., 1895, cxli. 128) make no mention of the importance of albumosuria in their analyses of the reported cases of multiple sarcoma or of allied affections of the bones.

In most of the diseases in which albumosuria has been found the albumose has been observed, as a rule, for a short time and in small quantity, although in rare instances for a long time and in large quantities. Pacanowski (*loc. cit.*) indeed subdivided the condition into acute and chronic albumosuria. But his distinction applied solely to the occurrence of the symptom in acute and in chronic affections. A more practical division is into transitory and persistent albumosuria. Transitory albumosuria is to be found, despite the faulty methods and the opportunities of error, in such a variety of diseases as to have proven of but little practical value except in the diagnosis of acute pneumonia, deep-seated suppuration, including meningitis, and macerated fœtus. In all of these conditions the ordinary means of diagnosis are usually sufficient, and the leukocyte count affords a most satisfactory aid and is an efficient substitute for the search for albumose.

Greater value is to be attached to the recognition of persistent albumosuria, the importance of which, in practice, has become especially suggested of late years in connection with the diagnosis of multiple but latent tumors of the trunk. Such an albumosuria is sometimes nearly a pure form, and is spoken of as primary or typical, better, perhaps, as persistent or excessive. This variety thus far has been observed principally in multiple bone tumors and in myxœdema, and in but few cases of these affections. These observations, however, are so suggestive as to demand general attention.

It has been my fortune in the past two years to have seen two cases of persistent and excessive albumosuria, so generally recognized as an exceedingly rare condition. The first case serves to introduce this communication, the second now in charge of my colleague, Dr. F. C. Shattuck, to illustrate it. In the latter the presence of albumosuria and its extreme degree led to the probable diagnosis of multiple tumors of the bones, and the use of the Röntgen rays showed such changes in the osseous structure as confirmed this opinion.

The source of the albumose in these cases may prove to be in the bone-marrow, as suspected by Virchow, but chemical analyses to de-

termine this point have yet to be made. It is also important that the subcutaneous tissues in myxœdema should be examined chemically for albumose, since the nature of the infiltrating substance in this disease is still a matter of conjecture, and the presence of albumose in the urine of two cases suggests a possibility requiring disproof even if the search give no other information.

Whatever the value of albumosuria may be in diagnosis, its persistent and excessive presence is apparently a sign of grave prognosis, since the cases in which this condition has been found have, almost without exception, proven fatal.

DISCUSSION.

DR. V. C. VAUGHAN: I simply want to say that this is an extremely interesting case, and it is very rare that such cases have been reported. The presence of small amounts of albumose is frequent, and, indeed, some claim that there is a small quantity of it in all cases of fever. So far as I know that is true, but the very large quantity demonstrated here is, I think, quite rare and is something like the cases reported years ago by Bence Jones.

DR. FITZ: Since the time of Bence Jones there have been reported some seven or eight cases of excessive albumosuria, almost all in German literature. It is obvious that since two cases have come under my observation within the last two years, the condition is perhaps more common than has been supposed. It is very easy to overlook the albumose, for in testing the acidified urine with heat the precipitate is ordinarily considered as albumin, but if the precipitate disappears by boiling, a more extended chemical analysis is likely to show the presence of albumose. This analysis can easily be made in a very few minutes.

DANGER OF ERROR IN DIAGNOSIS BETWEEN CHRONIC SYPHILITIC FEVER AND TUBERCULOSIS.

By E. G. JANEWAY, M.D.,
OF NEW YORK.

The subject which has been chosen for brief presentation before a medical body composed as this is must be defended by its recital as necessary, or else it would be presumptuous to take your time in the consideration of well-known diseases. A certain number of cases demonstrably of specific nature have come under my observation, condemned as being tubercular, not, as a rule, by physicians of little experience, but by those of well-established reputation, some being teachers and writers of medicine. Let us first pass in review the salient points of such cases, and you will bear in mind that from the nature of the subject more cannot be done.

The first of this group had been sent to a noted health resort for phthisical subjects; but instead of improving had steadily lost ground, so that after three months' trial he came to me reporting a loss of forty pounds in weight, a slight continued fever, a sense of weakness, and a pain in his right side. On examination this pain was found to be dependent upon a perihepatitis which was productive of distinct friction sound, with both inspiration and expiration, and also of palpable friction fremitus. An inquiry disclosed the fact that he had been a victim of syphilis ten years before. No proof could be found of any pulmonary lesion. Under antisyphilitic treatment in two months he had regained his weight, had lost the fever and malaise, and since that time has remained well. No doubt can be entertained that in this case the liver was the site of the specific processes which had been the cause of his hectic and of his ill health. Whether it would have been possible to detect the liver implication at a very early period I cannot determine; but he had seen two of the leading diagnosticians of this country in different cities, neither of whom had made out the

nature of his sickness, and by one of them he had been sent to the health resort for tuberculosis of the right lung.

A second case is that of an adult male who came to be examined because of fever, sweating at night, loss of weight, and pain in the right side. He had been ordered by a professor of medicine, who was also a noted examincr of diseases of the chest, to give up his business and remove to a resort for consumptives in consequence of tubercular disease of the right lung. A careful examination failed to reveal any distinct signs of focal pulmonary disease, but on more critical investigation two of the ribs on the right side were found to be sensitive to pressure, and a small sinus was disclosed in the neighborhood of the middle third of the right clavicle. He admitted syphilitic infection in early manhood. Antisyphilitic treatment removed his fever, and within a month he had regained his weight.

The third case relates to a patient who came to me with the history that he had been sent to a prominent health resort for consumptives because of the nexus of symptoms which have been detailed. After two months, stay there, he had been sent home, because of the continuance of his fever, and of his steady decline, which in the opinion of the physician there, thoroughly informed and capable, indicated miliary tuberculosis, for which there was no hopeful outlook. This physician had been frank enough to state that he could not satisfactorily locate the disease. My own examination was negative in so far as making out the location of a process which was productive of the disturbance of his health. This led to a cross-examination of the patient in regard to his antecedents. He admitted that he had had syphilis in the past. Under antisyphilitic measures he made a rapid improvement. Then he removed to another health locality, where a little over a year later he suffered from a synovitis of one knee-joint. The surgeons of the place considered this to be tubercular, and advised incision. He returned to me for advice. In addition to the effusion in the joint there was some thickening of the lower end of the femur. Again, under antisyphilitic treatment, within three weeks he had made such improvement as to be practically well, and has continued so since—a period of three years.

A fourth patient was referred to me for probable tubercular implication of the apices of the lungs, who had a rather marked cough in addition to the chain of symptoms outlined. Because no improvement

had followed a residence in a mountain resort near his home, and because of the steady decline in his health, and of the continuance of his fever for five months, notwithstanding the use of quinine and creosote, he had been ordered to a remote mountain region. He came to me to know if I could suggest any plan of treatment by which he could avoid the necessary sacrifice of his business interests should he act upon the advice given. The physical examination of the lungs was negative; such sputum as he could furnish did not contain bacilli of tubercle, neither did the examination of his body disclose any localization of morbid process which could satisfactorily account for the disease. A cross-examination elicited the history of a by-gone syphilitic infection. Within three days from the commencement of anti-syphilitic treatment his fever subsided; and he wrote me from his home, after the lapse of three months, that he had regained flesh, strength, and health. His letter closed with the inquiry, why his physicians had not resorted earlier to the use of a remedy which had proved so efficacious.

The fifth case was that of a young child who had continued fever, wasting, and a somewhat larger liver than his age warranted. The child had been treated with the idea of malarial infection in vain. The examination of the lungs did not disclose any sufficient evidence of tubercular trouble to warrant a diagnosis of that condition. A careful questioning was made as regards the possibility of tubercular infection through milk or contact, but without proof. The child was somewhat emaciated, and the examination of the abdomen failed to prove any enlargement of the glands. This led to a careful discussion of the case with the child's physician as regards the diagnosis, which, to my mind, lay between syphilis and tuberculosis. The enlarged liver inclined me to the diagnosis of syphilis, but I was assured that there was no possibility that either parent had had that disease, from personal knowledge; and I was dissuaded from making a cross-examination. The result was, that a diagnosis of probable tuberculosis was made. Later I was informed that, the child dying, an autopsy had revealed syphilitic infection of the liver, and the paternal parent had admitted a by-gone syphilis.

The sixth case is that of a male patient over thirty, now under treatment. He had syphilis ten years ago, and consulted me because of an urticaria which had come from eating stuffed peppers. He had

a very pale look, which was dependent on deficiency of hæmoglobin. The examination of the body revealed some enlargement of the liver and spleen. On inquiry, it was learned that he had lost thirty-five pounds, in the past two years, had sweats at night from time to time. The result of giving him a thermometer was to disclose the fact that he had a constant temperature which varied from 100° to 101½° for the most part, but on one occasion was 102°, and on another 104° F. during eight days of observation. There was more or less sweating at night. A careful examination of the lungs was made, with negative result. The blood showed neither plasmodia nor hyperleucocytosis. He was placed upon antisyphilitic treatment and five grains of quinine twice daily. Within a week he was much better. Less sweating and only very slight fever were noted. At the and of three weeks he reported that for a week he had not had fever. His weight had increased two pounds, and the examination show a distinct reduction in the size of the liver and of the spleen. Without administration of iron there had been, moreover, a distinct gain in his appearance, as indicative of improved hæmoglobin hold as the test by hæmoglobinometer.

To these could be added one other, were it not for the fact that an eruption appeared after weeks of fever, for which residence in a hospital, change of climate, and varied medication had been tried in vain. Specific measures produced a cure.

Cases likewise come under observation in which, with a history of past syphilis and a very limited area of lung implication, it can be hoped that the disease may be alone of specific nature. The most instructive case of this kind which I have followed through its course related to a man who came to me after a slight hæmoptysis. The only manifestation of pulmonary trouble was situated in the upper part of the lower lobe of the left lung. Here for a long time slight dulness, a little broncho-vesicular breathing, and a few sub-crepitant râles were all that could be made out. No bacilli were found in the scanty expectoration until one year from the attack and after he had been a resident of two health resorts. The disease spread in his case from the small beginning until the whole lower lobe was involved, a cavity formed, and the upper lobe of the same side affected. The question in such a case could be raised as to the nature of the process at its origin, and whether an original specific focus had become in-

fected by tuberculosis. It is, however, manifest that the physical signs enumerated would, in one without a history of syphilis, have been considered sufficient to establish a diagnosis of tuberculosis, considering the existence of hæmoptysis. Moreover, in this case, no impression was made by the employment of antisyphilitic measures.

The consideration of the facts here narrated have convinced me that many physicians are not aware that fever may attend the late manifestations of syphilis, more particularly of visceral syphilis. The neurologist is sufficiently alive to the importance of always considering the possibility of syphilis being an etiological factor in the obscure diseases of the nervous system, and he very generally gives the patient the benefit of a doubt, when uncertain, and attempts a diagnosis by the use of antisyphilitic measures. Moreover, the class of cases to which I have drawn your attention do not go to a syphilologist, but to the general or consulting physician, and this paper has been presented with the view of directing attention to the necessity of considering syphilis as a possible explaining cause of those obscure phenomena which are usually only considered to import tuberculosis, malaria, or sepsis. Moreover, I do not find that in the presentation of the subject, the syphilologist directs attention specific enough to the possibility here presented. Ignorance of the fact that syphilis, in what is termed its tertiary period, may occasion a fever of long duration, malaise, emaciation, perhaps perspiration, also, without of necessity presenting such definite local manifestations, either external or internal, as can be made out on such casual examination as often occurs when a patient seeks advice at the office of a consultant on one or a few occasions, is largely the explanation of the mistakes.

In two of the cases related it was not possible to state the situation of the diseaee after very careful examination. We must confess that not a few physicians are inclined with the above ensemblage of symptoms to determine that tuberculosis must exist; and having reached that decision, enough of that normal variation of physical signs will be made out to lead to the belief that the explanation has been found in certain pulmonary changes. Moreover, it has seemed to me that physicians having a strong belief that tuberculosis existed may have had an auditory illusion or hallucination. It is far wiser and better, to my way of thinking, to hold the mind in such a condition of attention in doubtful cases as shall admit of expression of doubt, than to attempt a positive diagnosis on insufficient data.

DISCUSSION.

DR. I. E. ATKINSON: As Dr. Janeway has said, there is nothing more striking than the want of active attention on the part of the medical community to the frequent presence of syphilis in all sorts of obscure diseases. It should be looked for in all obscure cases, especially in the class of cases Dr. Janeway has referred to. The presence of febrile conditions in the early forms of syphilis we are all prepared for, but in the late stages of the disease they are harder to explain. Where the fever presents a remittent character the conditions are extremely difficult to make out at times, and it is a little surprising that we do not more frequently recur to syphilis as the origin of the symptoms, since the results of antisyphilitic treatment are so decisive.

I have at present under my care a sailor who came from Calcutta to Baltimore without change of ship, who was taken sick some three weeks after going to sea, and had a continued fever. When he arrived in Baltimore he had a fever of distinctly remittent type, a diurnal range of from 3° to 4° F. being observed, and a greatly enlarged liver, the lower border reaching nearly to the navel. He had a cough, but no signs of pulmonary trouble, and the microscope did not reveal tubercle bacilli. The presence of albuminuria, the fact that he had been in India and denied syphilis led to the suspicion of hepatic abscess, as in one of Dr. Janeway's cases. He was aspirated several times. The plasmodium of malaria was excluded. Just before I came on duty at the hospital it was noticed that his left testicle had begun to enlarge. He was immediately placed upon iodide of potassium; within forty-eight hours his condition was ameliorated, and in a few days his fever had gone. He had fallen off many pounds in weight, and it was a case that exemplified in a most remarkable way the advantage of making use of antisyphilitic treatment in obscure cases.

I suppose we are all in the habit of recognizing cases of continued fever in the earlier stages of syphilis, but in these later cases, where the causes of fever are more apt to be obscure, we are more apt to look for tuberculosis than the real cause.

DR. S. J. MELTZER: The difficulty in diagnosis would seem to be still greater if we take into consideration the statement of Hansemann, that out of twenty-two syphilitic lungs there were only five in which he did not find the tubercle bacillus and some changes that looked like general tuberculosis. It seems, under these circumstances, that we must always give the patient the benefit of the doubt by treating him with antisyphilitic remedies, the more so as there are a number of statements in the medical literature to the effect that iodide of potassium and mercury are specifics in tuberculosis. The experience underlying these statements might have been derived from such cases as they have been described by Dr. Janeway.

DR. C. G. STOCKTON: I would like to ask Dr. Janeway if, from examination of the blood, he has arrived at a conclusion as to whether the temperature depends upon the toxæmia accompanying syphilis, or upon the secondary breaking down of gummata, or other local conditions. The matter was first brought to my mind four years ago in a case similar to those described, in which there was an intermittent fever supposed to depend upon tuberculosis. I attempted to differentiate by the tuberculin test. On injections of increasing strength, and finding nothing like a reaction, we concluded that the case was syphilis, and the man made a temporary recovery under antisyphilitic treatment. It would seem to me that the tuberculin test might be of advantage in differentiating. I should like to know from Dr. Janeway whether or not the blood in these cases, with temperature, was in any way different from the blood in the usual case of syphilis.

DR. V. C. VAUGHAN: I want to say one word in this connection, for I enjoyed Dr. Janeway's paper very much. I simply want to call attention to the fact that the two diseases may exist together, and do in a good many cases. I have had at least two cases recently of this kind where there was no doubt about the syphilis and tuberculosis existing in the same individual at the same time. I have noticed in these cases, though I cannot say how general it is, that the temperature-curve is different from that of tuberculosis, and I should like to know if others have observed anything of this kind.

DR. JAMES TYSON: Will Dr. Janeway tell us, also, the kind of syphilitic treatment employed, whether or not it was of the mixed character?

DR. JANEWAY: First, in answer to Dr. Stockton, I would say that examinations of the blood were made in some of these cases, but it it did not help us. The tuberculin test I did not use, the antisyphilitic treatment furnishing the test. Where we have the antisyphilitic treatment producing rapid improvement it is wiser not to use the tuberculin test, for I have had some cases that seemed to get rapidly worse after the use of this test, and in one case I had to dissuade a patient from entering suit against a physician for using this test.

The cases I called attention to were those where there was no mixture of diseases, though I have seen a number of such cases, but syphilis in its tertiary stage may have a fever that might be mistaken for malaria or tuberculosis, particularly the latter, and I called attention to this because in several of these cases a serious injury has been done the patient, or was advised to be done, by sending them to resorts for tuberculous invalids. I have made the paper brief and avoided details, because I recognized the fact that in dealing with the question of syphilis we have no right to introduce names of patients or places to which they have been sent, on account of the complications that might ariee. All of these patients are doing well, and it is the long duration since their appearance that has made me feel warranted in

saying that the treatment had been correct. In some of the cases I was not able to say, after a careful examination, where the lesion was.

The method of treatment employed was the mixed treatment, and I used the old preparation of tincture cinchona compound, bichloride of mercury and potassium iodide, giving ten grains of the iodide and one twenty-fourth grain of the bichloride three times a day. It has been very satisfactory in all of these cases.

DR. E. G. CUTLER: I should like to state, in regard to the question of Dr. Stockton, that I have seen no less than two cases of uncertain diagnosis where the tuberculin test led to the belief that tuberculosis existed, but where the subsequent post-mortems, made in one case by Dr. Councilman, and in the other, I think, by Dr. Wright, established the fact that it was an old syphilis, and not a particle of tuberculosis in the system. The tuberculin tests, though, were in both cases as positive as any I have ever seen.

DR. F. P. KINNICUTT: The form of fever which Dr. Janeway has described is certainly not of very infrequent occurrence in the tertiary period of syphilis and in the absence of appreciable physical signs of gross pathological changes. The insidious occurrence and progress of many of the lesions of this period is well recognized. Especially, perhaps, in the liver, do we find post-mortem evidence of old syphilitic inflammations, the patient not having exhibited symptoms referable to such lesions during life.

Simple gummata may exist in the capsule or in the substance of the liver, without causing pressure on ducts or vessels, and hence giving no physical signs of their presence. Their existence, however, may be supposed to be attended with more or less fever in individual cases; and again, this may be the case occasionally in interstitial hepatitis.

Comparatively lately I was greatly puzzled as to the nature of a remittent fever extending over a period of several weeks. The most careful and frequently repeated physical examinations failed to reveal the signs of organic disease. The possibility of tuberculous disease was considered and feared. Only on the development of severe nocturnal headache was the true nature of the symptoms suspected. The mixed treatment was immediately instituted, and at the end of a week the pyrexia disappeared, not to return. At the end of a month the patient's loss in weight, which had amounted to twenty pounds, had been made good.

PSEUDO-TUBERCULOSIS HOMINIS STREPTOTRICHA.

By SIMON FLEXNER, M.D.

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THE researches of the past quarter of a century have brought to light many species of micro-organisms, whose relation to certain pathological processes have been shown to be of the nature of cause and effect. Among these are included representatives from various groups, bacteria, protozoa, yeasts, and moulds. The greatest success thus far achieved has been in the study of the bacteria; indeed, until recently, these were regarded as almost the only vegetable micro-organisms capable of causing infectious pathological processes. Our knowledge of the biology of the pathogenic vegetable micro-organisms has more recently been extended in two directions. In the first, certain of the blastomycetes have been proven to be pathogenic for man and animals; in the second, the morphology of the bacteria has been found to depart from the simple formula originally assigned to them. In view of these facts it has been considered necessary to designate a new class for the reception of those vegetable micro-organisms which, while exhibiting affinities with the bacteria, at the same time possess certain features in common with the hyphomycetes. To this class Kruse has given the name *Streptothrices*. Its limits are ill-defined, chiefly for the reason that occasionally one of the common bacterial forms (B. tuberculosis, B. diphtheriæ, B. proteus) will show certain of the characteristics of the group, while for the most part they appear as simple rods.

The streptothrices resemble the moulds in that they develop from spores into cylindrical, dichotomously-branching threads, which alternately grow into colonies, the appearances of which suggest a mass of radiating filaments (mycelia). Certain of the threads become fruit-

hyphæ, and these break up into chains of round spore-like bodies. With the bacteria they agree in so far as they lack a doubly-contoured membrane, in not being composed of hyphæ filled with fluid and granular contents, and separated from each other by partition walls, and from the fact that they appear as homogeneous threads, resembling the filiform bacteria, which, finally, in older cultures, separate into short bacillary and coccus-like structures (Kruse).[1]

The researches of Boström[2] prepared the way for the later studies upon the micro-organism causing actinomycosis, and led finally to its classification with the streptothrices under the name of streptothrix actinomyces (Rossi-Doria). Another pathogenic species is represented by strephtothrix maduræ (Vincent). These two are the best known pathogenic forms; and an extensive study of their characteristics shows that it is not improbable that they may represent genera rather than species, so that ultimately it may become necessary to distinguish different species, or, perhaps, only varieties of each.

The remaining streptothrices described in connection with pathological processes in man are much less well defined. All the pathogenic possibilities of the class have not as yet been discovered. Rosenbach[3] found a branching micro-organism capable of growing upon artificial media and of reproducing upon inoculation a similar pathological condition, in an affection known as *erysipeloid* (Erythema exudativum multiforme). Eppinger[4] isolated from a brain abscess which had ruptured into the lateral ventricle and set up meningitis cerebro-spinalis, a branching micro-organism which he regarded as a cladothrix (C. asteroides), but which by Kruse is classed with the streptothrices (S. Eppingerii). Eppinger injected cultures into guinea-pigs and rabbits, and observed that it caused a typical pseudo-tuberculosis. Indeed, the cerebral abscess suggested the disintegration of a large tuberculous focus. The case reported by Garton is not so clear. This author obtained in pure culture a branching micro-organism from abscesses and a fistulous tract, extending from the upper dorsal vertebræ to the sacrum, the ribs and vertebræ showing erosions. While he regards the organism as a new species, its distinction from streptothrix actinomyces is by no means clearly established.

Additional instances of streptothrix infection are reported by Sabrazès and Rivière,[6] and by Ferré and Faguet.[7] The first case of Sabrazès and Rivière occurred in a man in whom abscesses were found

in the brain, lung, and kidney (softened infarction). The pus from the brain abscess showed single and radiating branching threads; in the kidney the filaments were much shorter, while in the lung neither form was discovered. In cultures cocci were found associated with the streptothrix, the latter growing anaërobically only. In a second case these observers isolated from sputa and from a subcutaneous abscess in a man an aërobic streptothrix, pathogenic for small animals. Ferré and Faguet obtained in pure cultures from an abscess of the brain in an epileptic a streptothrix which proved, however, to be non-pathogenic for guinea-pigs and rabbits.

It is now well known that under certain unusual conditions the bacillus tuberculosis is capable of appearing in an irregular branched form. Further observations are, however, necessary before accepting as final the results obtained by Friedrich[8] and Babès and Levaditi,[9] who inoculated cultures of the bacillus tuberculosis into the carotid artery and beneath the dura mater respectively in rabbits, and found that the bacilli had not only branched but had also developed into rosettes resembling the "drusen" of actinomyces.

Another streptothrix pathogenic for man is one upon which a preliminary note appeared in the *Johns Hopkins Hospital Bulletin*[10] for June, 1897, and of which the present paper will contain a more complete account.

A consideration of the morphology of the peculiar micro-organism which was associated with consolidation, necrosis, and early cavity formation in the lungs of a human being, and the nature of the pathological process which in so many ways suggested the caseous pneumonia of true tuberculosis, led to the adoption of the name *streptothrix pseudo-tuberculosa* for the organism, and *pseudo-tuberculosis hominis streptothrica* as a designation for the pathological condition.

The clinical history of the case offered nothing of especial importance.

The patient was a male, colored, aged seventy years, in whom extensive consolidation was made out in both lungs. The symptoms were broadly those characteristic of pulmonary tuberculosis. Sputum was carefully watched for during his stay in the hospital, in Dr. Osler's service, but none was obtained. No microscopical examination could therefore be made.

The autopsy was made nineteen hours after death, the body in the meantime having been kept on ice. No evidences of post-mortem decomposition

were noticeable. The description of the viscera is limited here to the organs which exhibited pathological alterations.

The *lungs* are voluminous and meet in the middle line anteriorly. They are not bound to the chest wall. *Left.* All of the upper lobe, except the anterior edge, is consolidated more or less perfectly. Where the consolidation is complete, as in the apical portion, the lung presents an opaque appearance, and is gray in color; beginning softening (disintegration with early cavity formation) is going on. These cavities often still contain the products of disintegration, and all appearances of reactive encapsulation are wanting. The lower zone of this lobe is more flaccid and contains scattered areas of consolidation, between which the lung tissue is œdematous and swollen, although not completely airless. The lower lobe is congested and œdematous; it contains a number of scattered and partly calcified nodules, which, on an average, are the size of a split pea. The pleura over the hepatized area is covered with a fibrinous exudate. *Right.* The middle lobe is almost completely consolidated. The other lobes contain several small calcified nodules and a number of recent, tolerably circumscribed, caseous areas, averaging in size that of a walnut, and surrounded by œdematous, imperfectly consolidated, and dark lung substance. The lower lobe contains an almost globular, infiltrated area, 4.5 cm. in diameter, caseous in appearance, the centre of which is undergoing disintegration. The pleura over the fresh foci of consolidation is covered with fibrin and studded with small hemorrhages.

Peritoneal Cavity. The intestines are moderately distended. The omentum is rolled up and thickened; it occupies a position beneath the transverse colon and extends across the abdominal cavity. The pelvis contains about 15 c.c. of fluid of a brownish color and mucilaginous consistence. Between the intestinal loops delicate threads of fibrin exist. In addition, smaller and larger nodules, resembling tubercles, usually translucent, are scattered irregularly over all the exposed peritoneal surfaces, and occur more uniformly upon and within the thickened, rolled-up omentum. The liver and spleen on section show similar nodules. The mesenteric glands are not perceptibly enlarged, but, upon section, minute opaque tubercles are visible in them.

Histological Examination. The microscopical study of the tissues of the case embraced all the organs. Reference will be made here only to the lungs, the peritoneum, and omentum, in which organs the chief lesions existed.

The pathological process in the lungs consists chiefly of an exudation, which is not, however, of uniform character. For the most part the exudate is cellular, but in certain situations it is composed largely of fibrin.

A stained section of the lung macroscopically presents a variegated appearance, due to this heterogeneous exudate. Where this is cellular a deep nuclear staining is evident; elsewhere the tissue appears pale. The cellular exudate is intra- and inter-alveolar; it is rare, indeed, that the alveolar walls are free from infiltration. The cells composing it are chiefly polymorphonuclear leucocytes, but what is most striking is the extent of fragmentation

which these cells have suffered. A small amount of fibrin exists among the cells. Many alveoli contain fibrin almost to the exclusion of leucocytes; this fibrin is dense and compact, and encloses cells of the epithelioid type. In certain situations, especially near the somewhat thickened pleura, the fibrin in the alveoli is undergoing rapid organization. The pleura is covered by a fibrinous membrane three or four times the normal thickness, capped by a thin line of dense fibrin in process of organization.

There is a marked tendency for the tissue showing the cellular infiltration to break down with formation of cavities showing softened contents. It is found that only where the infiltration of the alveolar walls has reached a high degree that this softening has taken place. But the gross examination of the lungs gave no adequate idea of the extent of this process of disintegration, many of the foci being microscopical in size. The disintegrating tissue differs from the general cellular infiltration only in containing more nuclear fragments and irregularly staining detritus. In specimens stained with hæmatoxylin and eosin, this irregular material takes on a peculiar imperfect hæmotoxylin tint, resembling certain kinds of caseation in tuberculous forms of pneumonia. In the regions in which the exudate is purely or largely fibrinous no such tendency to softening and disintegration is manifest. There is no attempt at limitation or encapsulation of the areas of cavity formation by a growth of demarcating connective tissue.

Circumscribed nodules having the size, form, and appearance of miliary tubercles occur in small numbers. They are composed chiefly of epithelioid cells, some of which are disintegrating. Giant cells were not seen.

The bands of interlobular tissue are thickened by a new growth of tissue, and islands of fibroid tissue appear here and there in the lung substance. The bloodvessels are extensively obliterated. This obliteration is caused either by an endarteritis or by thrombosis; sometimes both processes are met with in the same vessel.

Of the structures contained in the abdominal cavity, the intestine and omentum especially were subjected to histological study. Of these the latter gave the more interesting results. The thickening of the omentum is caused chiefly by a growth of tubercle-like nodules which cover its surface and also occupy its interior. The nodules are, on an average, larger than miliary tubercles, and still larger masses are formed by the coalescence of several such foci.

In general, two kinds of nodules are distinguishable. The larger, probably the more numerous, exceed in size a miliary tubercle; they are composed of a central mass of disintegrated or disintegrating cells and nuclei. Very irregular cell-forms are met with, some of these doubtless being emigrated polymorpho-nuclear leucocytes. Nuclear figures occur now and then among the degenerating cells, but these are taken to be examples of karyorrhexis, and not as representing true cell-division. Definite fragments of nuclei are common. The centre of such a nodule is occupied often by a transverse section of a small vessel, in which white blood-cells can be seen now and

then; the lumen is lined by endothelial cells, usually in increased numbers. Beginning at the thin outer wall, and often taking in everything except the endothelial cells, a homogeneous material may be noticed which extends for a variable distance into the tubercles proper, obliterating cell-boundaries as it spreads. With Weigert's fibrin stain this substance takes on a distinctly blue color. The more peripheral parts of the nodules contain more unaltered cells, these presenting the usual appearance of epithelioid cells, although mere elongated types (fibroblasts), and irregular leucocytes are also met with. The most external cells are lymphoid; and these, together with more or less polymorpho-nuclear leucocytes, go over into the surrounding adipose tissue and coalesce with other nodules. Giant cells appear in the less degenerated parts.

In the sections stained with hæmatoxylin and eosin a delicate fibrillated network can be made out among the cells and fragments which, in specimens stained especially for it, is found to consist of fibrin.

The smaller nodules differ from these in that they are made up of cells which are well preserved and possess large nuclei of the epithelioid type. The cell protoplasm is relatively abundant, and a suggestion of fibrillation is visible in the substance between the cells. This kind of nodule is found in the peritoneal covering of the intestines, where they form an almost uniform layer. Almost no degenerated cells are met with in these formations.

Giant cells are present within the nodules, but they are not abundant there, and they occur without these in the more diffusely infiltrated tissues. Their forms correspond with those found in ordinary tubercle, showing, as a rule, the peripheral disposition of nuclei and the central hyaline protoplasm. But multinucleated giant cells, either with peripheral or centrally massed nuclei, occur with especial frequency within the lumina of small blood- and perhaps lymph-vessels. It sometimes happens that such a cell occupies the central vessel in one of the first nodules described; but it is more common for them to appear in somewhat larger vessels outside, or just at the periphery of the nodules. They are derived from the endothelial lining of the vessels which is met with in the several stages of proliferative activity leading to their formation.

The Bacteriological Examination. The examination for bacteria consisted in the study of cover-slips from the fresh lungs, the inoculation of glycerin-agar tubes, and the subcutaneous injection into a guinea-pig of a suspension from the consolidated lungs. After hardening the tissues, sections from the lungs, peritoneal covering of the intestines, and omentum were stained for bacteria. Cover-slips from the lungs stained by Gabbett's method showed no micro-organisms which resembled the bacillus tuberculosis in their morphology, but there remained faintly stained in carbol-fuchsin upon the cover-slips numerous examples of a branching organism occurring often in the clumps or convoluted masses, among which no ordinary bacillary forms were discovered. Through the use of Weigert's method of staining bacteria the micro-organism was rendered suitable for more exact study.

The culture from the left pleural cavity and the peritoneum remained sterile. Three separate sets were made from the lungs. In all of these, at the end of twenty-four hours, a vigorous growth of a bacillus, identified as belonging to the group of B. coli communis, had taken place. The streptothrix did not grow.

The guinea-pig showed no reaction to speak of at the site of inoculation, the adjacent lymph-glands could not at any time be felt; the animal, however, lost in weight and died at the end of the ninth week, at the autopsy showing great emaciation. None of the lymphatic glands were found enlarged; there were no lesions resembling tubercles in these or other organs, and cultures upon glycerin-agar made from several sources remained sterile. Cover-slips from the serous cavities, blood, and viscera were negative for any kind of bacteria.

The further study of the organism stained upon cover-slips prepared from the lungs at the time of the autopsy by Weigert's method, in which carbol-fuchsin is substituted for gentian-violet, shows it to possess the following characteristics: The micro-organism appears only in streptothrix forms, rarely as single branching filaments, but usually as masses more or less convoluted, in which the several individuals seem at times to participate. This tendency to form convoluted masses renders the length of the filaments variable; some, however, stretch across the field of the microscope ($\frac{1}{12}$ inches objective). The thickness varies also, but to a less degree, and in general is about the same as that of the bacillus proteus. The branches are often short and rarely capped at the extremity with a conical swelling (conidia?). That these bodies are not actual conidia is, I think, further proved by their occurrence in the course of the filaments. They doubtless belong to the chromatic particles to be described later. There is protoplasmic continuity between the parent filament and the branch. The contours are slightly irregular, the staining sometimes not quite uniform, and very rarely just before its termination a filament will show two or three cross-partitions, suggesting the breaking up into as many short rods. Coccus-like forms were not encountered.

An irregularity in staining is one of the common features of the organism, an appearance, moreover, that depends in part upon the extent of the decolorizing process. The more deeply stained filaments are a little thicker than those which stain faintly, and the chromatic granules or particles which lie close together in the former may be separated in the latter by widths of unstained protoplasm of greater diameter than the stained particles. In the most pronounced cases the chromatic bodies appear to lie within a non-staining homogeneous membrane. (Plate I., Fig. 1.) The possibility that this difference may depend upon other causes—*e g.*. degeneration, cannot be excluded, but the impression obtained is that it is more or less artificial, and has something to do with the degree of staining, etc.

Sections from several different parts of the lungs were stained first in hæmatoxylin, and then in carbol-fuchsin, which was followed by pure aniline oil for the purpose of differentiation and dehydration. The nuclei

appear blue; the micro-organisms red. The latter are very abundant. Their relation to the pathological process is very intimate and somewhat as follows: The only parts of the lung tissue from which the micro-organisms appear to be absent are the areas occupied by the fibrinous exudate. The cellular exudate everywhere shows them, but the streptothrix is most abundant, appearing in the largest masses in the areas of rapid disintegration. (Plate I., Fig. 2.) The masses of the organism are somewhat larger than are met with in the cover-slips, and the branching is more perfect, perhaps because the normal relations are less disturbed in the sections. Rarely a small fragment of a filament or a separate thread will be present in a mass of pus-cells and fragments of cells. The streptothrix appears, but in relatively small clumps within the tubercle-like nodules; more often indeed a single branching filament is met with in these formations.

The staining of the threads is somewhat more irregular than in the cover-slip preparations; they present a granular, almost beaded appearance, and are thinner than under the former conditions. (Plate II., Fig. 3.)

The omentum especially, of the abdominal organs, was studied for micro-organisms. A large number of sections were treated first with carbol-fuchsin in the thermostat, and then carefully decolorized with 1 per cent. of hydrochloric-acid alcohol. Bacteria were never found in these specimens. Other sections were then stained by the method used for demonstrating the streptothrix in the lungs. Almost every specimen prepared in this way showed bacteria, and often in very considerable numbers. They were contained within the tubercle-like nodules.

The forms of micro-organisms met with in this situation are simpler than those in the lungs. So far as could be discovered from many sections the individual organisms never branch. They appear as rods of unequal lengths and curved or angular form. The staining is irregular, a beaded appearance being very common. The "beading" is quite irregular; more so, I am disposed to think, than is the case with the bacillus tuberculosis. In examples showing the most pronounced irregularity the organism appears as a nearly colorless filament with uneven deeply-staining red dots placed at different intervals from one another. In length as well as in width the rods rather exceed the average dimensions of the bacillus tuberculosis. It must, however, be admitted that not a few individuals could not be distinguished by the size alone from this micro-organism.

From the foregoing description there can be, I think, no reasonable doubt that the micro-organism encountered in the lungs differs widely from the known forms of the bacillus tuberculosis. This fact is also supported by the negative animal experiment described. On the other hand, it is equally clear that the pathological process set up by it in the lungs bears no little resemblance to one set of changes, at least, met with in the same organs in tuberculous pneumonias. We

notice in both cases the same tendency to infiltration of the framework of the lungs, degeneration of the inflammatory exudate, and to necrosis and solution of the tissues and exudate. In the particular case under consideration one point of difference is to be seen in the dearth of proliferated and desquamated alveolar epithelial cells within the exudate. But this difference is insufficient to characterize the two processes as essentially distinct. On the other hand, the impression is obtained that the solution of the exudate and framework of the lungs is going on more rapidly, from a greater number of centres, than is the case in ordinary cases of caseous pneumonia.

The analogy of the two processes is strengthened by the finding of tubercle-like nodules in the lungs amid the diffuse exudate. These were, it is true, few in number; but in structure they could not be distinguished from veritable tubercles, and they were proven to have been caused by the streptothrix under consideration, by the demonstration of the organism within them. It will be recalled that sections of the lungs stained for tubercle bacilli by the ordinary method failed to reveal the presence of this micro-organism.

When we come to consider the significance of the tubercles in the peritoneal cavity it must be admitted that the case in favor of their streptothrix origin is less clear and convincing. But I am inclined to the belief that they owe their presence to the same parasite which, however, owing to difference in the location and function of the parts, appears under somewhat different morphological forms. In view of the great numbers of micro-organisms contained within these nodules, it seems justifiable to conclude that they would have been demonstrated by the usual stains for tubercle-bacilli had they been of this nature. But I am unwilling to draw very wide-reaching deductions from this fact alone. The differences in morphology of the organism when compared with the tubercle bacillus may again be remembered, without, however, laying too much stress on small distinctions. Perhaps the most convincing argument is to be found in the existence of similar nodules in the lungs, whose etiology seems established. In these formations the organism appears under a simpler morphology than when growing freely within the lung-substance.

It would not be profitable, nor would it conduce much to a clearer understanding of the variation in morphology to dwell upon the influence of environment upon the growth and morphological character of

the bacteria; but it should be borne in mind that our knowledge of such variation is constantly increasing, and even now includes some of the commoner and more ordinary bacterial forms.

If in the comparison of the lesions in the lungs with those of caseous pneumonia sufficient proof has been brought of their great similarity to these, more conclusive evidence is at hand of the essential identity of the nodules in the peritoneal cavity with the tubercles caused by the bacillus tuberculosis. It is believed that upon histological grounds alone no distinction could be made.

From these considerations there can be little doubt that the streptothrix described is the cause of the pathological process met with in the lungs and peritoneal cavity, and, in the latter, that the pathological picture of the disease resembles so nearly tuberculosis in human beings that the two diseases can be separated only by the demonstration of the causative micro-organism in each case. It is, of course, not without the pale of probabilities that at some future time a clinical picture differing from that of true tuberculosis may come to be established for this disease.

If this conception of the pathological changes produced by the streptothrix under consideration be true, the process must be admitted to be a form of pseudo-tuberculosis in man for which the name at the head of this paper is proposed.

The question now arises whether a similar pathogenic streptothrix, producing analogous lesions, has thus far been described. There seems little doubt from the descriptions given of the pathogenic species of this organism in the introductory pages of this paper that the forms there mentioned differ from the one under consideration. At least no good grounds are at hand for concluding that in any case they are identical or even closely related. Not so, however, with the streptothrix described by Buchholz,[11] whose publication appeared simultaneously with the preliminary communication concerning the streptothrix pseudo-tuberculosa. It may perhaps be profitable to consider Buchholz's findings more in detail:

The patient was a steel-worker, thirty-eight years old, who became suddenly ill five weeks before admission to the Institute for Infectious Diseases in Berlin. He entered on November 19th, at which time there was absolute dulness over the entire right side of the thorax, with râles and bronchial breathing. The sputum showed numerous streptococci but no tubercle

bacilli. The fluid obtained by puncture from the plural cavity contained streptococci. On November 22d 300 c.c. of pus evacuated from the pleural cavity again showed streptococci. Death occurred on December 12th. The autopsy showed the right lung to be united throughout with the costal pleura; the left lung was bound to the diaphragm. The portion of lung corresponding with the adhesion to the diaphragm showed a consolidated focus the size of a hen's egg, which, on section, appeared to be necrotic. In the pleura covering the right lung were two formations which led directly into two large cavities, themselves communicating, filled with purulent contents and exhibiting ragged and uneven walls. The pus had a fetid odor; the remainder of the right lung, excepting the apex, was firmly consolidated. The rest of the organs showed no abnormality. The anatomical picture suggested an advanced tuberculosis, except that the edges of the cavities were more ragged. Tubercle bacilli could not be demonstrated; streptococci were, however, contained in the pus. The microscopical examination of sections was negative for tubercle bacilli; the histological picture, too, was regarded as showing differences from that of tuberculosis. The infiltrated parts of the lung presented more the appearance of an acute pneumonic exudate; but in places the interstitial infiltration was so marked as to obscure the structure, and the cells were undergoing necrosis (fragmentation, etc.). Stained by Gram's method, the firm, infiltrated, and necrotic areas showed a rich network of delicately branching threads of about the thickness of tubercle bacilli, which never appeared in the form of long bacilli, but suggested "lines sketched by the trembling hand or the snarled branches of the oak." Coccus-like and short bacillary forms were not found. The streptococci were contained in the portions of the lung which were consolidated, the alveolar walls being thickened and the alveoli in part atalectic. They were also present in the secretion of inflamed bronchi and in the interstitial lymph-spaces, from which situations the streptothrix was absent. The streptococci are regarded as having been secondary invaders. Cultures were not obtained from the lungs, the plates being overgrown with a variety of proteus. Animal experiments seem not to have been carried out. It is interesting to note that the same difficulty in staining the micro-organism was experienced as recorded in my case, and the most satisfactory preparations were obtained by the use of Gram's method, in which aniline-oil replaces the alcohol.

The resemblance of this case to the one described by me is very striking, but there are also points of marked difference. As regards the latter, the absence of all nodular formations suggesting tubercles and the extensive cavity formation in the right lung stand out in great contrast. On the other hand, it is conceivable that the cavities in Buchholz's case merely represent a later and more advanced stage of the condition present in mine. The description of the micro-

organism is strikingly like that given for the streptothrix pseudo-tuberculosa, and in the further support of their probable identity, I may mention that Dr. Rabinowitsch, who kindly carried slides of my case to Berlin with her, reports that Dr. Buchholz, after examining the preparations and comparing them with his own, regards them as probably identical.

At the last meeting of the Congress for Internal Medicine, held in Wiesbaden, Scheele and Petruschky[12] exhibited cultures and microscopical preparations of a pathogenic streptothrix obtained from a woman, aged fifty-six years, whose history in brief is as follows:

The patient gave a family history of tuberculosis, but had herself always been well. In November of the previous year she nursed a sister who died of tuberculosis. In February she suffered with what was supposed to be influenza; in March a cystitis developed, and about the middle of April several small tumors appeared in the skin about the joints, hip, sterno-clavicular, and, later, in the thigh, gluteal region, etc. The tumors suppurated. In the beginning of May the left upper lobe of the lung showed a fairly intense infiltration. The sputum was examined, but no tubercle bacilli could be found; on the other hand, masses of a "fungus" suggestive of penicillium were made out, and a similar organism was demonstrated in the pus from the tumors. The patient died on June 6th. The protocol is not given in this preliminary report. The micro-organism is, however, described as having been obtained in pure culture from the pus from the tumors; in the lung it was admixed with the bacillus influenzæ. In both situations it was abundant. The parasite is said to consist of fine, branching threads without showing any evidences of fructification. The complete description is reserved for a later publication.

In this instance it would be merely a matter of conjecture to consider that the lesions in the lungs and the streptothrix are similar or identical with those described by me; indeed, the clinical course of the case is not especially suggestive of similarity. The important consideration for the present is not to attempt a classification of the several pathogenic streptothrix forms now known, but to recognize their importance in human pathology, and more especially, that the lesions which they produce in the lungs may be suggestive of certain forms of pulmonary tuberculosis, both in their clinical course and anatomical appearances. Moreover, as the parasite is doubtless thrown off with the expectoration, it should be sought in doubtful cases in the sputa; and for this purpose the usual methods of stain-

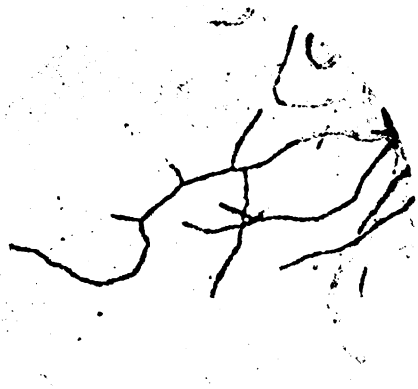

FIG. 1.

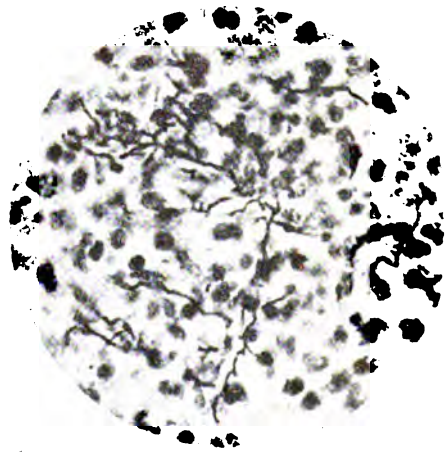

FIG. 2

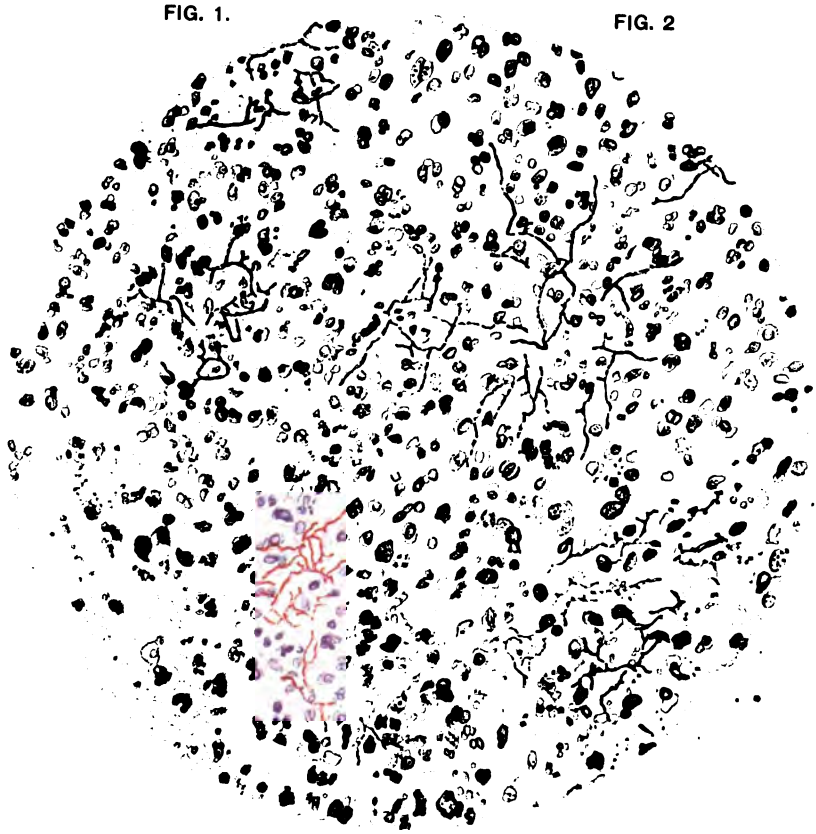

FIG. 3.

FLEXNER.—Pseudo-Tuberculosis Hominis Streptotricha.

ing for tubercle bacilli are not suitable. I should recommend the use of the modification of the Gram-Weigert stain, with which the parasite was demonstrated in smear-preparations and in sections.

I wish to thank Dr. W. M. Gray for the excellent photomicrographs which accompany this paper.

BIBLIOGRAPHY.

1. Kruse. In Flügge Die Micro-organismen, 1896, ii. 48.
2. Boström. "Untersuchungen über die Actinomykose des Menschen." Zeigler's Beiträge, 1890, ix.
3. Rosenbach. "Ueber das Erysipeloid." Archiv f. klin. Chirurgie, xxxvi. 346.
4. Eppinger. "Ueber eine neue pathogene Cladothrix und eine durch sie hervorgerufene Pseudotuberc. (Cladothrichica)." Zeigler's Beiträge, ix. 287.
5. Garton. "Ueber einen beim Menschen chron. Entzündung erregenden pleomorphen Mikroben." Zeitschr. f. Chirurgie, xii. 257.
6. Sabrazès et Rivière. "Sur un Streptothrix recontré dans un cas d'abcès du cerveau et d'infarctus supuré du rein." Le Presse Médicale, Sept. 22, 1894.
7. Ferré et Faguet, "Streptothrix et abcés du cerveau." Mercrede Médical, 1895, 441.
8. Friedrich. "Ueber strahlenpilzähnliche Wuchsformen des Tuberkelbacillus in Thierkörper." Deutsche med. Wochenschr., 1897, xxiii. 653.
9. Babes et Levaditi. "Sur la forme actinomycosique due bacille de la tuberculose." Archiv de Méd. exper., 1897, 1041.
10. Flexner. "Pseudotuberculosis hominis streptothrica." (A preliminary note.) Johns Hopkins Hospital Bulletin, 1897, vii, 128.
11. Büchholz. "Ueber menschenpathogene Streptothrix, ein Beitrag zur Ætiologie des akuten Lungenzerfalls." Zeitschr. f. Hygiene u. Infektionskrank., 1897, xxiv. 470.
12. Scheele u. Petruschky. "Culturen u. Präparate einer menschenpathogenen Streptothrix Art." Verhand. des xv. Cong. f. Innere Medicin., 1897, 550.

DESCRIPTION OF PLATES.

PLATE I.

FIG. 1.—Photomicrograph from smear-preparation from lung.

FIG. 2.—Photomicrograph from section of the lung. Both show the streptothrix: Fig. 1, free; Fig. 2, in intimate association with the exudation. Photographs by Dr. Gray, of Washington.

PLATE II.

FIG. 3.—Section of lung stained in hæmatoxylin and carbol-fuchsin. Zeiss 1/12 in. objective. The characteristic beading of the streptothrix is well shown.

AN EXPERIMENTAL STUDY OF THE DIRECT INOCULATION OF BACTERIA INTO THE SPLEEN OF LIVING ANIMALS:

And a Contribution to the Knowledge of the Importance of a Lesion in Animal Tissue for the Lodgement and Multiplication of Bacteria Within It.

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The methods of experimental infection which are at the present time mostly employed are subcutaneous or intraperitoneal inoculation, or intravenous injection of the micro-organisms employed. The final object to be attained is the introduction of the organisms into the circulation, and the different results obtained by these various methods of inoculation are largely due to a mechanical factor—*i. e.*, to the rapidity with which the organisms and their products are absorbed from the locality in which the injection was made.

It occurred to the writers that new characteristics in the forms of infection might be obtained from a systematic study of inoculations made primarily into one of the internal organs.

It seems fair to suppose that specific metabolic processes take place in all organs having special functions, and it is not illogical to assume that the specific catabolic processes of an organ might have a characteristic effect upon bacteria, more particularly when they are unchanged by previous contact with the blood or lymph.

The spleen, above all the internal organs, seems to harbor the specific micro-organisms in certain of the infectious diseases, and for this reason, notwithstanding the fact that the exact function of the

spleen seems to be little understood, this organ was selected for our experiments as the seat of direct infection. From its peculiar anatomical structure, some hold the opinion that the spleen acts as a filter and holds back bacteria from the blood passing through it. It might also be claimed that the bactericidal power of the blood was increased in the spleen, for on entering the organ, the blood, leaving the capillaries, comes in close contact with the lymphoid tissue where leucocytes abound, and it is generally believed that a close connection exists between leucocytes and the bactericidal action of body fluids.

Now, on the other hand, H. Buchner[1] claims that wherever disintegration of the red blood-corpuscles occurs the alexines fail to display their full power, and according to the prevailing opinion the erythrocytes are broken down in large numbers in the spleen, from which facts it might be assumed, as a fair hypothesis, that, while the non-corpuscular alexines are easily carried from the spleen by the blood, the corpuscular elements, including the micro-organisms, remain in in the spongy tissue of the spleen, and the bacteria, well nourished by the broken-down erythrocytes, resist the attacks of the remaining alexines.

Our first problem, then, was to determine the fate of bacteria when inoculated directly into the spleen.

The animals experimented on were chiefly rabbits, the inoculations were mostly of broth cultures of B. coli communis, and the results obtained were controlled by inoculations of broth cultures of B. typhosus and staph. pyogenes aureus. The inoculations, made with a hypodermatic syringe, were directly into the substance of the spleen, the needle being introduced into the ventral end—*i. e.*, that end of the spleen lying nearest the abdominal wall. The operation for exposing the spleen was made under ether anæsthesia, the incision in the median line of the abdomen causing little or no loss of blood. In none of our numerous experiments did a secondary infection of the site of operation occur, the wound in the abdominal wall healing *per primam.*

The slight bleeding from the spleen, caused by the puncture of the hypodermatic needle, was arrested either by a ligature thrown around the needle or by the actual cautery.

In due time each animal was killed with chloroform, and the autopsy performed immediately under strict aseptic precautions. After

[1] Cent. f. Bakt. und Parasit., B. vi. No. 1.

opening the thorax and abdomen the spleen was at once removed and placed in a sterilized Petri dish, and cultures were then made in 10 per cent. nutrient gelatin, reacting 1.5 per cent. acid to phenolphthalein, from the blood in the left ventricle, hepatic vein, liver, and left kidney, as a routine procedure; other cultures being made from time to time as hereafter noted. Gelatin plates were then made from the spleen, which, for convenience, was divided into three parts: the ventral end, or that through which the inoculation was made, being designated I, the middle third being designated II, and the dorsal third was designated III. Three large "loops" of the juice of the spleen were used for making the plates, and other plates were made with bits of tissue torn out from the substance of the organ. All plates were kept under observation for not less than seven days. Cover-glass smears were also made from the tissues plated.

EXPERIMENT 1.[1] Medium-sized rabbit, 5 minims of twenty-four hours' broth culture of B. coli communis injected into the spleen. Autopsy after forty hours. Plates from Parts I, II, and III of the spleen remained sterile.

EXPERIMENT 2. Small rabbit; 6 min. of forty-eight hours' broth culture of B. coli com. injected into spleen. Autopsy after forty hours. Spleen plates, I showed 4 colonies; II, 2 colonies; III, 5 colonies. Plates from liver, 6 colonies; from hepatic vein, 2 colonies, and from left ventricles, 4 colonies.[2]

EXPERIMENT 3. Small rabbit, 6 min. of twenty-four hours' broth culture of B. coli com. injected into spleen. Autopsy after fourteen hours. Spleen plates, I, 3 colonies; II, 7 colonies; III, no colonies. Plates from liver, none; from kidney, 1 colony.

EXPERIMENT 4. Large rabbit, 10 min. of twenty-four hours' broth culture of B. coli com. injected into spleen. Autopsy after fourteen hours. Spleen plates, I, 11 colonies; II, 43 colonies; III, 3 colonies. Plates from liver, 32 colonies; from hepatic vein, 15 colonies; from left ventricle, 133 colonies; and from left kidney, no colonies.

EXPERIMENT 5. Small rabbit, 5 min. of twenty-hours' broth culture of B. coli com. injected into spleen. Autopsy after three hours and twenty minutes. Spleen plates, I, no colonies; II, 13 colonies; III, 3 colonies; plates from liver, 2 colonies; from hepatic vein, no colonies; from left ventricle, 5 colonies; and from left kidney, no colonies.

EXPERIMENT 6. Small rabbit, 25 min. of four-days' broth culture of B. coli com. injected into spleen. Rabbit died in three and a half days. Autopsy

[1] The experiments are numbered in the order in which they are reported, not in the order in which they were made.

[2] The number of colonies reported are the average of two or more plates made from the same locality, the number occurring on each of the several plates not being far from the average obtained.

six hours after death. Spleen plates, I, 200; II, 350; III, 150 colonies of B. coli com.; no other colonies present.

EXPERIMENT 7. Large rabbit, 25 min. of forty-eight hours' broth culture of B. coli com. injected into spleen. Plates from the three parts of the spleen, from the liver, hepatic vein, left ventricle, and left kidney all remained sterile.

It seems unnecessary to mention further experiments of this kind, the few here quoted from our protocols show that large numbers of bacteria injected into the spleen soon disappear.

The organisms injected into the spleen were neither kept back mechanically, as in a filter, nor did they find within the spleen a soil favorable to their multiplication. Although the 5 minims of broth culture which were injected correspond to about one-third of the entire volume of the spleen and contained many millions of bacteria, the plates made from the juices and tissue of the spleen were for the most part sterile, and even in the plates made only three hours and twenty minutes after the inoculation but few colonies developed. Controls of the cultures employed for the inoculations were made in several instances by adding a small loopful of the culture to 5 c.c. of sterile broth and immediately plating three loopfuls of this mixture in nutrient gelatin. The number of colonies developing on these plates varied from 3000 to 10,000.

These control experiments assured us that many millions of bacteria disappeared from the spleen within a short time.

The question now arose: Is this large number of bacteria rapidly destroyed in the spleen, or are these bacteria carried out from the spleen in immense numbers by the blood current?

The best method to exclude the latter proposition would have been to tie all the splenic veins, but this we could not do in the small animals experimented with. In a single case an attempt was made to prevent the flow of blood from the spleen by tying the portal vein.

EXPERIMENT 8. Medium-sized rabbit; ligated portal vein and then injected 5 min. of broth culture of B. coli com. into the spleen. Animal died in thirty minutes. The spleen was removed, placed in a sterilized Petri dish and plated fourteen hours later. Juices and tissue were plated from five different incisions made into the spleen. All plates showed an innumerable growth, and no contaminations were found.

In the other experiments it seemed preferable to tie the splenic vessels themselves, but we were obliged to ligate the arteries together with veins.

EXPERIMENT 9. Large rabbit; tied all splenic vessels and injected into the spleen 5 min. of broth culture of B. coli com. Autopsy after forty hours. Spleen plates I, II, III, all show an innumerable growth of B. coli com.

Here the bacilli could not migrate into the circulation, and, indeed, there was every evidence of an active growth of the bacilli within the spleen. We had to remember, however, that the supply of fresh blood, and with it the supply of fresh alexines were cut off, while the amount of alexines present in the spleen at the moment of ligating the vessels was probably out of proportion to the number of bacteria introduced into the spleen. It is now generally accepted that the effect of the bactericidal elements in the blood is but little apparent in the presence of large numbers of bacteria, and that after the bactericidal powers are exhausted the surviving bacteria multiply with great rapidity.

Anatomists teach that the capillaries in the spleen resolve and the blood enters the tissue; and the assumption seems justified, and is indeed tacitly made, that quite a fair communication exists between the interstitial spaces of the spleen. We therefore resorted to the plan of ligating only a part of the vessels pertaining to the spleen, anticipating that the migration of bacteria from the ligatured portion would be considerably restricted, while there might be some, perhaps an abundant supply of the bactericidal factors to this part, provided by the neighboring parts of the spleen through which the blood was allowed to flow.

EXPERIMENT 10. Small rabbit; tied about one-third of the vessels on the ventral end of the spleen, and through the ventral (ligated) end injected 5 min. of a twenty-four hours' broth culture of B. coli com. into the middle portion of the spleen. Tip of spleen tied. Autopsy after forty hours. Tip of spleen was found detached from the rest of the organ and embedded in the mesentery; the ventral third of spleen, the vessels of which were ligated, was considerably thickened and paler than the remaining part of the organ, and distinctly separated from it by a ridge or line of demarcation. The plates made from the ligatured part of the spleen (I) were overcrowded with colonies, and the plates from Parts II and III showed growth of colonies which were too abundant to count. Colonies were most abundant in plates from Part I, distinctly less abundant in plates from Part II, and still less numerous in the plates from Part III.

EXPERIMENT 11. Medium-sized rabbit; bloodvessels of the ventral third of spleen ligatured and 6 min. of a broth culture of B. typhosus injected

through the ventral end into the middle third of spleen. Autopsy after forty hours. The ligated end of the spleen was hard, dark red, and dull on the surfaces, and the hard portion was separated from the normal part by a sharp ridge. Spleen plates: I, innumerable colonies; II, 1900 colonies; III, 1150 colonies. Plates from liver developed 91 colonies; from hepatic vein, 90 colonies; from left ventricle, 20 colonies, and from left kidney, 4 colonies of B. typhosus.

In some experiments in which the vessels of the middle portion of the spleen were ligated and the animal was allowed to live for seven or eight days, the entire middle portion of the spleen had become very much thickened, of a grayish-yellow color, and remarkably dry, while both ends of the organ, the circulation of which we endeavored not to interfere with, appeared normal in every respect.

Thus we see that our expectation of a collateral interstitial nutrition was not realized, an interesting fact, which, however, we cannot discuss further here.

On the other hand, our experiments showed that plates from the non-ligated portions of these partly ligatured spleens developed a considerable number of colon or typhoid colonies, quite in contrast to our experience with spleens no part of which was ligated.

In studying over our entire material, it seemed to us that the assumption which gives the fittest interpretation of all the facts in our possession—at least for the present—is that: 1, the blood within the spleen is less bactericidal than the blood within the balance of the circulation, due, perhaps, to the nourishment afforded the bacteria by the large numbers of disintegrated erythrocytes within the spleen; and 2, the structure of the spleen offers but little hinderance to the rapid migration into the circulation of large numbers of bacteria injected into this organ.

Our experiments, which showed that but few bacteria could be found in the spleen only a few hours after large numbers had been injected into it, must be explained by assuming that great numbers of them were soon carried out from this organ through the splenic veins by the blood-stream; the fate they met was probably that which awaits those large numbers of bacteria which are injected directly into the circulation.

In our second set of experiments, in which the bacteria were injected into a spleen part of the vessels of which had been ligated, the presence of bacteria in the non-ligated portion of the spleen may be

explained by assuming that many of the bacteria which got into the ligated part remained there, and, from the abundance of nutriment, multiplied rapidly. From this source a fresh supply of bacteria was constantly given out to the adjacent non-ligated part of the spleen, where the blood flowing through the organ carried the bacteria out almost as soon as they were supplied to it.

Although it seems to be a fact that but little interchange of nutritive fluids takes place between the several regions of the spleen, the bacteria are apparently able to wander over by their own motility (colon and typhoid) or to grow through from one region into another.

The fact that only a few hours after injection into the spleen so few bacteria could be found in the blood does not argue against the assumption that all the injected bacteria were carried out into the blood-stream, because they disappear in the same manner when injected directly into the veins.

Wyssokowitz[1] found, five hours after injecting 1 c.c. of typhoid culture into the jugular vein of a rabbit, that 0.2 c.c. of the blood contained only 5 bacilli.

The presence of 1900 colonies in plates made from a point in the spleen adjacent to a part the vessels of which had been tied, while not more than 90 colonies were found in plates made from the liver and the hepatic vein, may well be interpreted in favor of the assumption that blood within the spleen is less bactericidal than blood in the vessels nearest to the spleen.

Another point in favor of this assumption seems to be the fact that the bacteria thrive in a ligated spleen, while, according to de Giaxa and Guarnieri,[2] bacteria succumb to the bactericidal effects of blood in the vessels between two ligatures, as well as in the extravascular blood.

Finally, we have to report that in a number of cover-glass smears made from non-ligated spleens which were most carefully examined microscopically, no bacilli were discovered; and it would seem to us improbable, even if only a considerable portion of the bacteria were killed by the alexines, that no bodies of the bacteria which would take a stain should be found in the smears.

The views here put forward would seem not be in harmony with

[1] Wyssokowitz, Zeitschrift für Hygiene, vol. i. [2] Annales de Micrographie, 1890.

the statements of Wyssokowitz.[1] This author found, after injecting numerous micro-organisms into the jugular vein, that they soon disappeared from the circulation, but that a number of them settled in the spleen, liver, and bone-marrow, a fate which, according to Ponfik[2] and others, they share with non-organized corpuscular bodies, such as cinnabar, ultramarine, etc., injected into the circulation.

Wyssokowitz, however, states further that certain bacteria, like the typhoid bacillus and others, soon become destroyed within the spleen. He states that twenty-four hours after the injection of the typhoid bacillus into the blood, cultures made from the spleen show no living bacilli; in other words, he claims that the spleen acts as a filter upon the organisms in the blood passing through it, and the bacilli succumb to the bactericidal influences within the spleen.

With regard to the first point, we freely admit that corpuscular elements may find within the spleen a greater obstacle to their free movement than in any other part of the blood-current, and that a larger accumulation of organisms may occur in the spleen than in any other part of the circulation; yet the results of our experiments prompted us to assume that the retained bacteria are easily carried out again from the spleen and that the "filtration" is comparatively of but little account and not permanent. As to the disappearance of the bacteria from the spleen, we maintain that Wyssokowitz has not offered the slightest proof of his assumption that the destruction of the bacteria occurs within the spleen; this disappearance of the bacteria can be as well explained by supposing that they have been gradually carried out from the spleen by the blood into the vessels, where they have succumbed to the bactericidal power of the circulating blood. However, we wish it understood that we by no means claim that the spleen possesses no degree of bactericidal influence and that no destruction of bacteria takes place in this organ. On the contrary, at the beginning of our experiments the total sterility of the inoculated spleens led us to believe that the bacteria were destroyed by the bactericidal elements of the spleen; and when during our investigations the highly important publications of R. Pfeiffer[3] and of A. Wasserman[4] appeared, showing that the elements of active immunization in

[1] Loc. cit. [2] Virchow's Archiv, 1869.
[3] Pfeiffer and Marx: Deutsche med. Woch., 1898, p. 47.
[4] Berliner klinische. Wochens., 1898, p. 209.

cholera and in typhoid fever appear in the greatest amounts in the spleen, lymphatic glands, and bone-marrow, and inasmuch as immunization in typhoid fever and in cholera does not mean antitoxic but bactericidal effects, we were further strengthened in our belief that we, too, had found bactericidal effects of remarkable power within the spleen; yet a careful analysis of the results of all our experiments led us to the present conclusion: that the bactericidal power within the spleen acts rather less intensely than in the rest of the circulation.

As a matter of fact, this view seems to us to harmonize far better with the principles and findings of Ehrlich, Pfeiffer, and Wasserman. The normal bactericidal elements are not identical with the bactericidal bodies of active immunization; they are derived from different sources. The bactericidal elements of the normal blood are seemingly generated in one way or another by the leucocytes, while Pfeiffer has established the fact that the bactericidal bodies generated by immunization stand in no relation to the leucocytes. Following the theory of the so-called "side-chain-immunity" of Ehrlich,[1] it is assumed by Behring[2] and by Wasserman that these bactericidal bodies are generated by the organ-cells, which, reacting to certain stimuli, produce an excess of these bodies. The stimulating agents are the bacteria and their products.

This, in a few words, is the essence of the views of these writers so far as concerns us here. We believe now that we are not going too far when we add the hypothesis that the greatest over-production of the bactericidal bodies occurs in those organs in which the bacteria are permitted to multiply most actively. In other words, when the bactericidal elements of the normal blood are less active, less influential, then the most active generation of bactericidal bodies of immunization takes place. It is in this sense, then, we can claim that our assumption of the diminished effect of the normal bactericidal action within the spleen harmonizes with the statements of Pfeiffer and of Wassermann: that the bactericidal bodies of immunization are abundantly produced within the spleen. In one of our experiments with injections into the non-ligated spleen numerous bacilli were found to be present in the liver.

In this case an attempt had been made to reach the vagus nerve below the diaphragm, requiring some pressure upon the liver, and it

[1] "Die Werthbemessung des Diphtherieheilserums." Klinisches Jahrbuch, vol. 6.
[2] Deutsche med. Wochens., 1898, No. 5.

occurred to us that the mechanical injury the liver had received might have been the cause of the retention and, perhaps, multiplication of the bacteria within it.

We therefore attempted to produce by cauterization circumscribed lesions of the surface of the liver before injecting bacteria into the spleen, and our experiments in this line show conclusively that by mechanical injury to the tissue we have it in our power to cause bacteria which are circulating in the blood to settle in any part of the surface of the liver we may select. In all the cases experimented upon the cauterized part of the liver contained innumerable organisms; in the normal part of the organ immediately adjoining the lesion they were still numerous, while in remote parts but few, if any, were to be found. The organisms found in the lesions were pure cultures of the species which had been injected into the spleen. In cases where the animal was allowed to live for thirty to forty hours, it was easy to establish the fact that an innumerable quantity of bacteria were present in the lesion, while none were found at the site of inoculation. The perfect sterility of the spleen and the immense number of bacteria found at the site of the lesion showed that at least some of the bacteria migrated from the spleen in a living condition.

The liver, however, is the next station at which bacteria escaping from the spleen would arrive, and the question suggested itself whether a sufficient number of bacteria escaped from the spleen to allow of their reaching and settling in a more remote organ, and whether or not lesions of other organs would react in a similar manner to those of the liver.

To this end lesions were produced by cauterization in several organs: in the kidney, the uterus, the testicle, and in a circumscribed area in the peritoneum and in subcutaneous tissue, etc. In all places where suitable lesions were produced the specific organisms were present in large numbers, as illustrated by the following experiments:

EXPERIMENT 12. Large rabbit; cauterized pregnant uterus through incision in abdomen, and injected 2.5 min. of a three-days' broth culture of B. coli com. into spleen. Autopsy after three and one-half days. Spleen plates: I, 1 colony; II and III, 0. Plates from liver, 0; from hepatic vein, 1 colony; from left ventricle, from left kidney, 0; from the site of lesion in the uterus and from the fluid in the cavity of the uterus at site of lesion, innumerable colonies.

In this experiment the quantity of culture injected was small, the rabbit and the spleen were both large, and the plates made from the blood and uninjured organs were sterile—conditions which would favor the interpretation that the bacteria were all destroyed in the spleen, but the abundant growth in the lesion of the uterus demonstrates that a considerable number of bacilli must have escaped into the general circulation to found this thriving colony in a remote region.

EXPERIMENT 13. Medium-sized rabbit; cauterized right kidney and uterus, and injected 5 min. of a three-days' broth culture of staph. pyogenes aureus into the spleen. The tip of the organ through which the needle was inserted was tied. Autopsy after forty hours. Spleen plates from tied tip showed 460 colonies, from Part I, 192 colonies; Part II, 7 colonies; Part III, 4 colonies. Plates from the liver, hepatic vein, left ventricle, and left kidney were sterile; from the right kidney, necrotic portion and adjoining portion, innumerable colonies; and from the necrotic portion of the uterus over 10,000 colonies developed. The tip of the spleen contained a considerable number of bacilli, as did also the adjoining part, a fact which was observed in nearly all the experiments in which the tip of the organ was tied, and which probably is explained by cutting off the blood-supply by the ligature.

Our observations on the action of bacteria in lesions made in the internal organs seemed to be of such importance that we conducted a series of experiments by injecting bacteria into the general circulation, after producing lesions in one or more of the internal organs.

EXPERIMENT 14. Large rabbit; ventral end of spleen and border of liver squeezed with hot forceps; 25 min. of a twenty-hour broth culture of B. coli com. injected into ear vein. Autopsy after forty hours. The cauterized portions of the spleen and of the liver were necrotic. Plates from the blood in left ventricle showed 1 colony; from left kidney, 0; from hepatic vein, 48 colonies; from normal part of liver, 2 colonies; from the necrotic part of the liver the colonies were innumerable; from Part I of spleen, the necrotic portion, innumerable colonies; from Part II the colonies were also innumerable but distinctly less than were found in Part I, and from Part III but 39 colonies developed.

EXPERIMENT 15. Large rabbit; cauterized right kidney, border of liver, two areas in spleen (one near each end), a circumscribed area of the peritoneum, and the subcutaneous tissue in the right inguinal region. Twenty-five min. of a broth culture of B. coli com. were then introduced into the ear vein, and the animal was killed after sixty-four hours. Plates made from blood in left ventricle showed no growth; from hepatic vein, 0; from a normal portion of the liver, 0; from necrotic part of the liver, innumerable colonies;

spleen plates showed an innumerable number of colonies from the necrotic portions of a very abundant growth, though distinctly less from the intermediate parts; plates from the left kidney showed no growth, while those from the normal part of the right kidney showed 410 colonies; the development from the necrotic portion of the right kidney and the apparently healthy tissue adjoining it was innumerable, though distinctly less in the latter case than in the former. Plates made from the cauterized portion of the peritoneum and from the necrotic subcutaneous tissue all showed an innumerable growth.

EXPERIMENT 16. Medium-sized rabbit; squeezed with hot forceps the ventral end of the spleen, the lower border of the liver, and the lower end of the right kidney. Twelve min. of broth culture of B. coli com. were then injected into the ear vein. The autopsy was made after forty-one hours, and plates from blood in the left ventricle developed no colonies; from hepatic vein, 72 colonies; from normal part of liver, 570 colonies; from the necrotic part of this organ, innumerable colonies; from an adjoining portion, 2671 colonies; from the left or normal kidney, 0; from the squeezed portion of the right kidney, innumerable colonies. Plates made from various parts of the spleen developed very few colonies.

The few colonies found in plates from the spleen may perhaps be explained by the fact that the squeezed portion of the spleen was dry and leathery in appearance and very tough when cut into, and it may be that the circulation was so completely cut off from this part that the bacteria had but little chance to reach the lesion in the organ, and were mostly carried out again into the circulation. It seems probable that the bacteria can gain access to the injured tissue and be deposited there only when some more or less normal tissue remains within the necrotic part—*i. e.*, tissue through which the blood may flow. It is, of course, a very difficult matter always to regulate the amount of pressure exerted so as to produce the same kind of a lesion in every experiment.

In this connection it seems important to mention that in experiments in which half of the vessels of the spleen were tied and the inoculation made into the circulation through the ear vein, plates made from the spleen, whether from the ligated or the non-ligated part, remained sterile. The sterility of the ligated portion probably finds its explanation in the reasons set forth above. Injections made directly into or through a ligated portion of the spleen offer entirely different conditions, for here the bacteria are brought directly into the ischæmic part, and could not escape except through their own motility or by growing out through enormous multiplication. It

seems likely that the abundant growth within the ligatured portion of the spleen was due largely to the lesion of the tissue caused by ligating the vessels, which favored the retention and development of the organisms.

The principle underlying the fact that a lesion in an organ favors the retention and development of bacteria within it is not new. J. Rosenbach,[1] Becker,[2] and others have shown that the intravenous injection of staphylococcus pyogenes aureus would cause osteomyelitis in a fractured bone. The experiments of Wyssokowitz[3] and of Prudden[4] have established that a mechanical lesion, and, according to Prudden, that also a chemical lesion of the cardiac valves causes the staphylococcus and the streptococcus when intravenously injected to settle there and develop ulcerative endocarditis.

According to Wyssokowitz, however, the M. tetragenus and other organisms did not settle in the injured valve. In our experiments with the three species of bacteria mentioned we made no attempt to determine how they would act in relation to the injured heart-valves, but were enabled to cause them to settle in any tissue experimented with, by producing a suitable lesion. This seems to us a point of great practical importance, inasmuch as any physiological or artificial injury, such as parturition or operation, carried out under the most scrupulous asepsis, can become infected if in any place in the body there exists a focus containing micro-organisms—and in this connection it must not be forgotten that attenuated micro-organisms may regain their virulence in a tissue lesion.[5] How many cases of puerperal infection or of post-operative asepsis might here find their explanation? Without, however, entering into a discussion of the numerous instances in pathology which can be interpreted profitably by our facts, we would add that, judging from a few experiments we have made, it would appear that lesions of the internal organs can become infected also from a subcutaneous focus.

In one experiment in which subcutaneous injection of the B. coli com. was employed, plates made from the injured portion of the liver contained over 2000 colonies, while the necrotic spleen showed a very meagre growth.

[1] Zeits. f. Chirurgie, vol. x.
[2] Deutsche med. Wochens., 1884.
[3] Virchow's Archiv, vol. 108.
[4] Amer. Journal of Med. Sciences, 1887, p. 70.
[5] Nocard and Roux. Annales de l'Inst. Pasteur, 1887.

In another similar experiment the plates from the necrotic portion of the spleen contained over 6000 colonies, from a cauterized portion of the peritoneum about 1000 colonies, and in plates from the cauterized uterus there were innumerable colonies.

The failure of Wyssokowitz to produce ulcerative endocarditis from subcutaneous injections of pyogenic bacteria may perhaps be explained by the fact that certain bacteria are but slowly absorbed from the subcutaneous tissue; if the injury to the valves had been caused a few days after the injection, instead of simultaneously, more time would have been allowed for the bacteria to get into the circulation, and the result might have been different.

The frequent mention of the presence of B. coli com. in the cauterized portions of the liver might lead to the suspicion that this ubiquitous organism was present in the liver before the intrasplenic or intravenous injections were made. Aside from the numerous instances in which the uninjured organs were found free from this bacillus, other studies bearing directly on this point were made. A number of rabbits were opened, the liver and spleen were cauterized, and the abdomen closed, just as in the other operations alluded to, but without any injection of micro-organisms whatever. After a few days the animals were killed and plates made immediately from the injured and uninjured organs and from the blood, and in all the cases the plates were found to be sterile. It therefore seems to us probable that the cases in which numerous colon bacilli were found in the normal liver were from platings made some time after death had occurred.

In conclusion, we desire to say that, although in our many experiments we have produced numerous foci containing very many bacteria, and thus have offered a number of different sources for the abundant supply of bacteria to the blood, the blood, nevertheless, has remained perfectly sterile or contained very few bacteria. The blood is also a liquid tissue, and we may perhaps assume that the blood, too, like other tissues, permits the growth of bacteria within it only when it is in some way injured.

Conclusions.

1. Cultures of B. coli communis, B. typhosus, and staph. pyogenes aureus when injected into the tissues of the normal spleen soon

disappear from that organ, and, indeed, from the normal body generally.

2. Bacteria injected into a spleen after the whole or a part of the vessels have been tied multiply in the spleen with great rapidity, and continue to supply bacteria to the blood, where, in the healthy body, they soon disappear.

3. Bacteria injected into the spleen or subcutaneous tissue or into the blood-current through the ear vein, in cases where moderate lesions have been made by cauterization or compression in the spleen, liver, kidney, uterus, testicle, peritoneum, or subcutaneous tissue, usually find lodgement in these lesions and multiply there.

4. Even in cases where numerous foci existed from which the blood was constantly provided with a fresh supply of bacteria but few bacteria were found at any time in the blood.

DISCUSSION.

Dr. W. H. Welch: Drs. Meltzer and Cheesman's contribution to the doctrine of locus minoris resistentiæ by their observation that bacteria settle and grow in damaged areas of the body is welcome because, this doctrine has been attacked, especially by Rinne. Drs. Meltzer and Cheesman thus confirm the view generally held by bacteriologists as well as by practitioners. Their conclusion that bactericidal substances are less abundant in the spleen than elsewhere hardly seems to be positively demonstrated by their experiments. The partial or complete ligation of the splenic bloodvessels seems to me to introduce such factors, especially alterations in the integrity of the spleen, that the preservation and development of pathogenic bacteria in the organ under these circumstances, in contrast with their rapid disappearance from the normal spleen, hardly justifies the inference that the normal spleen is notably lacking in bactericidal powers.

Dr. A. Jacobi: Dr. Welch has already alluded to the evidence given by practitioners to some of the statements made by Dr. Meltzer. It is certainly true that bacteria will locate where the tissues are no longer healthy, being damaged by some process or other. Where the tissues are normal we do not find bacteric invasions. It is certainly a fact that diphtheria, for instance, will not locate in a healthy throat, but always requires a damaged epithelium, except, perhaps, where the normal epithelium of the tonsil is broken by interstices, as pointed out by Hoch; there it may enter, but otherwise it always requires an injured surface. What occurs in the circulation appears

to illustrate the same thing. We know, for instance, that tuberculosis will settle in the ends of the bones where the circulation is slower. In the epiphyses, particularly of the young, and when the epiphysis is the seat of rhachitical hyperæmia, it is more apt than a normal epiphysis to allow the tubercle bacilli to be deposited.

These are two examples that I have seen so often in my life that they occurred to me while listening to Dr. Meltzer's demonstrations. Then there is another question, How is it that there should be the great difference in the appearance of the spleen, or rather in the number of bacilli found in the spleen, on one hand, and in the circulation of distant parts, on the other hand? I believe one of the reasons why they are found more or less in the circulation of distant parts is given clinically by the condition of the spleen itself. The spleen is not a stable body. Its size changes very often during the course of the day, and that influences the relative amount of blood and blood-contents in the circulation of the spleen. Other instances of changes in the blood and their effects on the circulation are given by the following facts: I think we all know of the occasional occurrence of the first attack of an intermittent fever after the administration of a large dose of quinine. I think that observation has been made a great many times; surely I have seen it confirmed a number of times in my own experience. A person is suffering from chronic malaria, has never had a chill, he is given a large dose of quinine, and the first response to that is a very severe chill. Why should that be so? I think it is because the quinine produces contraction of the spleen, which becomes squeezed out like a sponge, forcing a great deal of blood with the plasmodia into the circulation; thus a chill is produced. I have noticed the same thing after the administration of ergot in chronic malaria. I have seen a marked and good effect in unconquerable malaria by the use of ergot, but in a few instances after giving a large dose of ergot the attack would at first become more severe than it had been. I believe it was for the reason given, viz., that the circulation became filled with cells that had been idle. This should be taken into account while considering whether injections into the spleen will be tolerated by the organism or will have any favorable results.

DR. MELTZER: With regard to the explanation Dr. Welch has given to the fact of the growth of bacteria within the ligated spleen, we ourselves have given the same explanation in a part of our paper which I did not have the opportunity to read. Our conclusions were not based upon the presence of bacteria in the ligated part of the organ, but on their presence in the non-ligated portion, and on the further fact that in a spleen, no part of which was ligated, no bacteria were found there. We have adduced in our paper many more reasons for our assumption that the spleen is less bactericidal than the blood. At the same time I acknowledge that we ourselves do not consider that we have proven this point beyond doubt. We tried to express ourselves carefully by saying that this assumption is the fittest explanation of all the facts we had at hand.

In regard to the other point raised by Dr. Welch, that our statement that in any part where we have produced a lesion we could find a settlement of the bacteria which we had injected into the spleen or ear vein is only a part of the old rule of the locus minoris resistentiæ, it seems to me that our experiments show something more than that. It is not a question of more or less resistance; our experiments rather tend to show that the bacteria never settle in living tissue, but always in an injured one.

THE BACILLUS ICTEROIDES (SANARELLI) AND BACILLUS X (STERNBERG).

By GEORGE M. STERNBERG, M.D., LL.D.,
SURGEON-GENERAL, U. S. ARMY.

I REGRET that a scientific question of the deepest interest should be complicated by the necessity on my part of correcting certain erroneous statements made by Dr. Sanarelli in his papers published in the *Annales de l'Institut Pasteur* (No. 6, 1897) and in the *Centralbl. für Bacteriol.*, Dec. 22, 1897.

Dr. Sanarelli says in his first paper published in the *Annales* of the Pasteur Institute:

"Dr. Sternberg, of Baltimore, author of the most recent, the most rich, and the most methodical contribution to this disease known up to the present time, declares that the specific microbe of yellow fever is yet to be found, and he affirms that the whole question is to be taken up *ab initio*."

This is not exactly my position, as witness the following quotation from the introduction to my report:

"I have now commenced writing a report, because I feel that an account of what I have been doing during the past two years is due, and not because I have brought my investigation to a successful termination, or because I feel that there is nothing more to be done.

"No one can regret more than I do that the question of the etiology of yellow fever is not yet solved in a definite manner, but I, at least, have not to reproach myself with want of diligence or failure to embrace every opportunity for pursuing the research. The difficulties have proved to be much greater than I anticipated at the outset. If the task before me had been to find an organism in the blood, like that of relapsing fever, or of anthrax, or an organism in the organs principally involved, as in typhoid fever, or leprosy, or glanders, or in the intestine, as in cholera, the researches I have made could scarcely have failed to be crowned with success. But this has not proved to be the case, and among the micro-organisms encountered there is not one which by its constant presence and special pathogenic power can be indisputably shown to be the specific agent in this disease."

Note that I say "among the micro-organisms encountered there is not one which, by its constant presence and special pathogenic power, can be shown *indisputably* to be the specific infectious agent in this disease." But I carefully described one particular bacillus, and, in summarizing my results, said: "It is possible that this bacillus is concerned in the etiology of yellow fever." Evidently it was my intention that subsequent investigators should consider this possibility, and if my work was well done, by approved methods, no one has a right to ignore it; and continued investigations by the same methods cannot be considered as taking up the question *ab initio.*

Again, Sanarelli says: "Sternberg thinks that there is probably a localized infection having its principal seat in the *stomach.*" This is a mistake. I have advanced the hypothesis that the germ of yellow fever may perhaps be located in the alimentary canal, as is the case in cholera, and that the symptoms result from the absorption of a very potent toxin produced by it. But this is only a suggestion, and I know of no evidence indicating that there is a localized infection of the stomach.

These mistakes might be excused, but it is difficult to attribute the following misleading quotation from my report to a simple mistake. In his recent paper, published in the *Centralblatt für Bakteriologie* (p. 672), Sanarelli says:

"Je dois cependent signaler que dans son 'Report,' le même Dr. Sternberg ne s'exprime pas d'une facon telle; à propos d'un cas, assez confus, il dit ceci, à la page 200: 'En un seul cas, j'ai obtenu le bacille x, en une culture du foie du cobaye 179, inoculé avec 3 gouttes de matériel obtenu du foie d'un tuberculeux, et conservé pendant 48 heures sous une enveloppe antiseptique. L'animal succomba le 6 jour après l'inoculation et je retirais du sérum recueilli dans le tissu conjonctif sous-coutané, un bacille présentant tous les caractères du bacille x. La culture de ce bacille en eau de noix de coco, tua le lapin 205 en 7 heures (3 ccm.) et le lapin 207 en 4 heures (2.5 ccm.).' *Cette circonstance élimine le bacille x de toute considération ultérieure comme agent étiologique possible de la fièvre jaune.*"

The unfairness and misleading character of this attempt to rule bacillus x out of court is shown by that portion of my report which immediately follows the quotation made by Sanarelli, which is as follows:

"This seemed to exclude bacillus x from further consideration as the possible etiological agent in yellow fever; but upon referring to the history of

this guinea-pig I found that it had been inoculated a week previously with a culture of bacillus x (one-half cubic centimetre injected subcutaneously, November 20, at 10 A.M.)."

In the case of guinea-pig 179 bacillus x was evidently present in the tissues at the autopsy because it had received a subcutaneous inoculation of one-half c.c. of a pure culture of this bacillus a week before it was inoculated with the crushed liver-tissue of a tuberculous case. But this fact is suppressed by Dr. Sanarelli. To test the question as to whether bacillus x could survive for some days in the tissues of an inoculated guinea-pig, I made the following experiments:

"December 17, 1889, 9 A.M. Injected subcutaneously into guinea-pig No. 189, 1 cubic centimetre culture bacillus x in *agua coco*. The animal remained in apparent good health, and was killed at 11 A.M., December 23. Cultures were made from its liver and spleen; in both bacillus x was obtained in pure culture.

"The experiment was made in duplicate; 1 cubic centimetre of the same culture having been injected into guinea-pig 190. The animal was killed at the same time, and cultures made from the liver and spleen contained bacillus x."

Again, Dr. Sanarelli makes the following statement with a view to discredit my work:

"Ceci est probablement dû à une circonstance qui m'a été signalée par quelques médecins qui ont suivi à la Havene les recherches du Dr. Sternberg; il paraît que celui-ci n'examinait pas lui-même les malades et ne pratiquait pas lui-même les autopsies, mais faisait ses recherches sur la matériel cadavérique, qui lui était apporté à son laboratoire privé, par les médecins chargés des nécropsies dans les hôpitaux militaires."

It is true that I did not personally examine and make clinical notes upon the sick in hospital who were subsequently the subjects of my autopsies. But it is false that "I did not myself practise the autopsies, but made my researches upon cadaveric material brought to my private laboratory by the physicians charged with necropsies in the military hospitals."

I did not make clinical notes because I had no time, and because I had previously had an extended clinical experience in three epidemics in the United States,[1] and had been a member of a commission sent to Havana to investigate yellow fever in 1879. I, therefore, went to

[1] Governor's Island, 1870; Fort Barancas, Fla., 1873 and 1875.

Havana as an expert, and considered myself entirely competent to confirm the diagnosis of yellow fever, made by the Spanish medical officers in charge of the cases, by the pathological appearances found at the autopsy. I, myself, suffered a severe attack of the disease in 1875.

In Havana when a death occurred in the military hospital the medical officer of the day sent a messenger to inform me of the fact, and I went as promptly as possible, sometimes alone and sometimes accompanied by my assistant, Dr. Martinez, or by Dr. Burgess. More than once I left the dinner-table to make an autopsy, and frequently I went alone at night, and had no other assistance than that of the Spanish soldier who had charge of the room in which the dead were kept. Occasionally I had the assistance of some other physician in making the autopsy, but I invariably collected the material for my bacteriological researches myself. This is clearly stated in my published report, which Dr. Sanarelli evidently has in his possession.

Again, Dr. Sanarelli says:

"En plus, les microbes isolés ainsi, sans une règle constante et sans uniformité de méthode et de vues, étaient expérimentés chez les animaux d'une façon tellement sommaire que l'importance et les caractères spécifiques du microbe de la fièvre jaune, auraient dû forcement échapper à l' attention du Dr. Sternberg, même si le bacille ictéroïde avait fait acte de présence parmi sa nombreuse collection bactériologique. Et il ne pouvait pas en être autrement, si l'on considère que l'auteur a fait à la Havane, dans l'espace de 4 mois (mai-août) et au milieu des nombreux inconvénients d'une température tropicale et d'un laboratoire improvisé, l'étude bactérioiogique de 45 cadavres: c'est à dire, plus d'un cadavre tous les trois jours!"

This misrepresentation of the facts as set forth in my published report is unworthy of a scientific man. I say in my report:

"The investigations to which this report relates were made in the city of Havana in the summers of 1888 and 1889; in the city of Decatur, Ala., in the autumn of 1888, and in the laboratories of the Johns Hopkins University, where I have continued my researches during the intervals between my visits to the infected localities, and since my return from Havana, in September, 1889, up to the present date."

My first autopsy was made in the city of Havana, May 12, 1888, and my report was submitted June 21, 1890. My investigations, therefore, covered a period of over two years, and of my 43 autopsies 10

were made in Havana in May and June, 1888; 3 in Decatur, Ala., in October, 1888; and 30 in Havana between the 23d of April and the 26th of August, 1889. One of my 43 cases (No. 28) in which the diagnosis of yellow fever had been made was excluded, as is shown in my record of cases.

It is true that in 1889 my autopsies followed each other so rapidly during a portion of the time (month of August) that it was impossible to make a complete bacteriological examination. and I did not attempt to do so, but devoted my attention especially to material obtained from the liver, upon the supposition that any micro-organisms present in other organs or in the blood would probably be found in this organ, which is the subject of such profound pathological changes.

I ceased to collect blood from the heart after my nineteenth autopsy. All these facts are fully set forth in my report, and the results of my culture experiments are stated in detail.

Having invariably found various bacteria in great numbers in pieces of yellow fever liver kept in the incubator for twenty-four hours or longer and enveloped in an antiseptic wrapping, I endeavored to isolate and study these by the usual culture methods, and to ascertain by comparative experiments whether any one of them was to be found only in the liver of yellow-fever patients. I collected material from the liver at every autopsy, and from the liver only in a considerable number.

As Sanarelli's bacillus grows readily in the culture media employed by me, I infer that it was not present in the yellow fever cadavers which were the subject of my researches, unless it is identical with one of the bacilli encountered in my investigations.

At least, I think, the scientific world will agree with me that if identity be disproved further researches by independent investigators will be required to demonstrate that bacillus icteroides is the specific germ of yellow fever, and competent bacteriologists should be able to find this bacillus in typical cases of yellow fever occurring in Havana as well as in those infected localities in South America which have furnished the cases studied by Sanarelli. For myself, I may say that I shall be extremely glad to see the question of the etiology of yellow fever settled in a definite manner, even if it should turn out that I have been mistaken in the supposition that Sanarelli's bacillus is identical with my bacillus x, and if the final verdict of the scientific

world accords me no share in the honor of discovering the specific infectious agent of this pestilential disease which has been the subject of my special studies for many years.

The explanation offered by Sanarelli to account for his failure to find his bacillus in a considerable proportion of the cases examined by him does not appear to me to be satisfactory. He says:

"Its isolation often presents almost insuperable difficulties, due in part to the constant occurrence of secondary infections, and in part to its relative scarcity in the organism."

In the series of cases studied by me secondary infections were extremely rare. The colon bacillus was found in a number of cases, but usually in comparatively small numbers, and there is no good reason for believing that the fatal result depended upon its presence. But for the fact that in the second case studied by Sanarelli his bacillus was present in considerable numbers in blood extracted from the finger of the patient the evening before his death, and also, after death, in the blood, spleen, liver, and other organs, it is quite probable that his attention would not have been attracted to this particular bacillus. In this regard this case is unique, both in the series of cases investigated by Sanarelli and in those studied by me; and if this is indeed the bacillus of yellow fever, it is evident that it is usually present in the blood or tissues of yellow fever patients in very small numbers, or not at all.

This is shown by the fact that I did not once obtain it—unless it is identical with my bacillus x—in my cultures, into which I introduced blood taken from one of the cavities of the heart (19 cases), or crushed liver tissue (42 cases) collected as soon as possible after death.

As stated in my previous paper, my information relating to Sanarelli's bacillus when this paper was written was obtained from a translation in the *British Medical Journal* of his address given before the University of Montevideo, June 10, 1897. I have since read his paper in the *Annales* of the Pasteur Institute, and upon my return from Europe in September I passed through Paris, and through the courtesy of Dr. Roux obtained a culture of the "bacillus icteroides" which had recently been sent to the Pasteur Institute by Dr. Sanarelli. I now recognize the fact that there are certain cultural differences, some of which have been pointed out by Sanarelli in his paper in the

Centralblatt für Bakteriologie. At present bacillus x is non-motile, while Sanarelli's bacillus is actively motile. But in my original cultures, as stated in my published report, bacillus x was motile. The presence of flagella may now be demonstrated by proper staining methods.

In judging of cultural differences now existing, it must be remembered that bacillus x has been cultivated in artificial media for eight years. In the comparative study now being made in the pathological laboratory of the Army Medical Museum in this city the peculiar seal-like colonies, to which Sanarelli attaches so much importance, have not been observed in cultures of bacillus x. Again, bacillus x causes gas-production in lactose bouillon, while Sanarelli's bacillus does so in less degree or not at all.

In view of these facts complete identity in biological characters cannot be maintained.

The next question which arises is whether the bacillus obtained by Sanarelli from yellow fever cadavers in Rio de Janeiro and by me from yellow fever cadavers in Havana are varieties of the same species. Comparative experiments are now being made under my direction with a view to determining this question.

In my opinion bacteriologists are often too much inclined to differentiate species upon slight cultural differences, such as the appearance of colonies, ferment action, etc. Sanarelli himself has shown us, in his paper published in the *Annales* of the Pasteur Institute, three varieties of the colon bacillus which may be distinguished by differences in the colonies formed upon gelatin-plates. Every experienced bacteriologist knows that varieties of all the best known species of bacteria exist and that these may differ as to their pathogenic power, the rapidity and character of their growth in various culture media, their power to produce pigment, the production of acid, of gas, etc.

If bacillus x and Sanarelli's bacillus icteroides are not even varieties of the same species, the question will remain whether one, or the other, or neither, is concerned in the etiology of yellow fever.

It is evident that neither has a claim worthy of serious consideration upon any other ground than that which relates to its pathogenic action. Sanarelli's claim is based chiefly upon his inoculation experiments upon the lower animals and upon man, and his results deserve the most careful consideration. Comparative experiments upon dogs,

rabbits, and guinea-pigs are now being made, under my direction, with Sanarelli's bacillus and with my bacillus x. These experiments have been performed in the pathological laboratory of the Army Medical Museum by Major Walter Reed, Surgeon, U. S. A., in charge, assisted by Dr. James Carroll, Hospital Steward, U. S. A., and the results will be reported in detail in a paper by Dr. Reed to be published as soon as he has completed his researches.

EXPERIMENT 13. July 23, 1897, 1.20 P.M. Young dog, No. 327, weight, thirteen pounds, inoculated into ear-vein with 5 c.c. of a twenty-four-hour culture in glucose bouillon of x from blood of rabbit 314, a very active, lively animal. 1.35 P.M., appears very sick—lying down—does not respond to voice. 2.05 P.M., vomits considerable quantity of partially digested food, followed by fluid stool, with tenesmus. 2.23 P.M., small, brown watery stool. This repeated at short intervals, with much tenesmus. 2.51 P.M. and 3.05 P.M., vomits, with much effort, a small quantity of grayish frothy fluid mixed with mucus 3.30 P.M., vomits. 4 P.M., dog lies on its side with extremities rigidly extended. Temp. in rectum 104.1° F. Prior to injection, temp. 101° F. July 24th, 9 A.M., temp. 102° F., refuses food or drink. Lies on side with extremities extended. During the day has several thin, dark, fluid stools containing blood and mucus. 4 P.M., temp. 104° F. Died at 6 P.M., twenty-eight and a half hours after inoculation.

Autopsy. Thorax: Thymus gland large, dark red; shows a number of small hemorrhages beneath surface. Mediastinal glands swollen, dark-red in color. A small hemorrhage over right auricle, which is distended with blood. Left auricle empty. Right ventricle distended, left contracted. Hemorrhages beneath endocardium in latter. Valves normal. Myocardium pale red.

Numerous hemorrhagic areas beneath pleura over right lung. Both lungs, all lobes, congested. Lower lobe right lung œdematous. On cut section reddish fluid exuded freely.

Abdomen: Numerous hemorrhages beneath peritoneal surface of duodenum.

Liver: Of a mottled, pale and red color, the light color predominating.

Spleen: Enlarged, dark red, firm.

Kidneys: Enlarged, cortex swollen, pale.

Adrenals: Small, pale.

Stomach: Mucous membrane over greater curvature of uniform, dark-red color. No erosions to be seen.

Intestines: Duodenum and upper part of jejunum contain considerable quantity of a fluid, black, tarry material. Mucous membrane of small intestine pale throughout. Peyer's patches not swollen.

From ileo-cæcal valve to anus the longitudinal rugæ of mucous membrane are the seat of marked hemorrhage which extends into submucosa. Some fluid blood in large intestine.

Bladder: Contracted, containing about 4 c.c. of albuminous urine. Cultures from blood, liver, and spleen show numerous colonies of x. Kidney, urine, and bile negative.

Microscopic examination of sections show widespread necrosis, with fatty degeneration of liver parenchyma and cloudy swelling of renal epithelium.

EXPERIMENT 35. August 6, 1837. Dog No. 347. Weight, ten pounds. Injected at 2 45 P.M., with 13 c.c. of a seventy-two-hour culture in 2 per cent. lactose bouillon of x from rabbit No. 338. Animal much prostrated by injection. 3.05 P.M., vomits food with much retching; again vomits at 3.15 P.M., followed by watery stool containing mucus. Temp. 4 P.M., 96.4° F. Prior to injection rectal temp. 101° F. Found dead at 8 o'clock following morning, less than eighteen hours.

Autopsy. Thorax: Subendocardial hemorrhages in left ventricle. Subpleural hemorrhages, upper lobe, right lung. Hemorrhagic infarct lower lobe, same lung.

Abdomen: Liver pale, grayish color.

Spleen: Slightly swollen, dark red, soft.

Kidneys deeply congested.

Stomach contains about 200 c.c. of fluid blood. Mucous membrane throughout of a dark-red color. Both small and large intestines contain much fluid blood. Mucous membrane of small intestine swollen and of a uniform dark raspberry red. Less injection of large intestine, though this is quite marked. Bladder contracted, empty.

Cultures positive from blood, liver, spleen, and urine. Negative from bile and kidney.

Microscopic examination of sections of liver show cloudy swelling of cells, with congestion of capillaries.

These experiments show that bacillus x injected into the circulation of dogs produces symptoms and pathological lesions similar to those produced by equal quantities of a culture of Sanarelli's bacillus. The persistent vomiting, intestinal hemorrhage, albuminous urine (dog 327), and profound changes in the liver-cells are certainly very remarkable, and give additional weight to the supposition made in my report that "it is possible that this bacillus is concerned in the etiology of yellow fever." (P. 272).

Dr. Reed reports the following results with reference to the Widal reaction:

"Agglutinative reaction of icteroides serum on bacillus x.

"Serum prepared by Sanarelli and received from Dr. Archinard.

"Dilutions of 1 : 150 give satisfactory agglutination of x at expiration of one hour.

"Reactive influence of x serum upon bacillus icteroides.

"Dog 520. Immunization begun November 29, 1897, serum drawn April 15, 1898.

"Dilutions of 1 : 300 promptly arrest motility of bacillus icteroides and bring about good agglutination at end of one hour."

A dog immunized to bacillus x received 25 c.c. of a recent culture of bacillus icteroides in a vein, and at the end of five days 40 c.c. Was not seriously affected, and remains in good health.

DISCUSSION.

Dr. A. C. Abbott: I would like to ask Dr. Sternberg if parallel experiments have been made with the colon bacillus or any of its modifications, to see in how far the results would correspond to those obtained with the bacillus x and the bacillus icteroides? I have had the opportunity recently of seeing the cultures of Dr. Archinard, and have had quite a wide experience with the colon bacillus within the last year. From Dr. Sanarelli's report and from our studies of Archinard's micro-organism the differences between them and the colon group are qualitative rather than quantitative. I feel personally that Sternberg's and Sanarelli's bacilli are identical, for I do not believe that slight quantitative differences are sufficient to identify them as distinct species.

Concerning the question of pathogenesis, one observes among the members of the colon group striking differences in the degree of this property; but in the nature of the lesions produced there is little difference, and they are strikingly like those resulting from inoculation with bacillus icteriodes and bacillus x.

Dr V. C. Vaughan: I do not know a great deal about this subject, but my colleague, Dr. Novy, began work on the Sanarelli bacillus about a year ago. He worked for four months with Roux at the Pasteur Institute, and then, after coming home, continued his work. His results will soon be published; but from what I have seen of his work I am convinced, and I think he is, that there is no proof whatever that Sanarelli's germ is the cause of yellow fever.

The experiments that Sanarelli made upon men are simply ridiculous, if we take them as evidence that this germ is the cause of yellow fever. He injected the toxin into patients (I suppose they were patients, for they were in the hospital), and he got marked effects, and jumps to the conclusion that it was yellow fever. There are many germs the toxins of which may, on inoculation, produce "marked effects," and we cannot conclude from such an experiment that the germ is the specific cause of any disease.

It has always seemed to me since Dr. Sternberg's most excellent work upon the subject that the probabilities are that yellow fever is not due to bacteria. Of course, we may be mistaken, but I think that if it had been due to such a cause Dr. Sternberg would have discovered the organism. I have a great deal of faith in the clinical belief of our brethren in the South that yellow fever never hibernates in cold countries. I do not know Dr. Sternberg's opinion upon this point, but he will remember that our old friend, Dr. Cochrane, held such views and defended them with great tenacity at the Yellow Fever Congress of 1889. Long-continued freezing of Sanarelli's germ does not affect its virulency. You may leave it frozen for a great many days, and yet when thawed out it is just as virulent as at the start.

Sanarelli's observations on agglutination were some of them made in a test-tube. He added some of the germs to serum in a test-tube, watched it, and saw the lumps form. It is perfectly absurd to study agglutination in that way. The blood of the students in the University of Michigan—I do not think any of them ever had yellow fever or anything like it—causes agglutination of Sanarelli's germ. We know it is a highly motile germ and agglutinates very rapidly in various kinds of serum. I do not want to anticipate Dr. Novy's paper, and I am sorry he is not here to speak on the subject himself; but these are some of the things I have gathered from his work. I do not think that there is the slightest evidence that Sanarelli has discovered the cause of yellow fever. In one of his articles he says that he has had yellow fever, but in a recent article Havelburg, who has given up his own claims to become an advocate of Sanarelli, states that Sanarelli has been vaccinated against yellow fever.

Dr Wm. Osler: I would like to ask Dr. Sternberg how much stress he would lay upon the Widal work done by Archinard during the recent epidemic. That has seemed to me to be one of the most favorable pieces of work for the Sanarelli bacillus, for they obtained their bacillus icteroides directly from Sanarelli, I believe, and claim that in fifty cases of yellow fever they found the reaction very satisfactory.

One other point that has been referred to I should like to mention—that is, the question of experiments upon men, as they were brought forward prominently in Sanarelli's paper. They have been characterized by Dr. Vaughan as ridiculous, but I beg to say that is not the term to use. The limits of human experimentation should be clearly defined in our minds. From a clinical standpoint almost every dose of medicine we give is an experiment. Who knows what may happen from giving a 2-grain dose of quinine to a child? It may die, as did one of Dr. McKenzie's children. To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal.

Dr. Sternberg: With reference to Dr. Abbott's question, I will say that I have felt all along that we wanted some comparative researches with patho-

genic colon bacilli. We have not come to that point yet in our laboratory, but shall do so soon. When I came through Paris Dr. Roux was not impressed with the view that Sanarelli's alleged discovery would turn out all right. He spoke of the symptoms of vomiting, etc., in the dog, and said he knew there were various bacteria that would cause similar results. I do not want to reject the possibility that this may be the yellow-fever germ without giving it very careful study. It has always seemed to me that it is not improbable that this pestilent disease of the West Indies may be, according to Park's idea, a fæcal disease. I think it is not at all impossible, while of course beyond proof, that the typhoid bacillus is an offshoot from the colon bacillus at some past time, and it is not unreasonable to suppose that another pathogenic variety of the colon bacillus may produce this pest. Evidently yellow fever is a toxæmia and not a septicæmia. The results show that, as does the clinical history and pathological study. You know it was a good while before we found the typhoid bacillus in every case examined, and it was only after learning how and where to look for it that its constant presence in the spleen and intestinal glands was demonstrated. Now, in the case of a bacillus which produces such a deadly poison as this—Sanarelli showed that 5 c.c. of a filtered culture produced such a marked effect that two or three of his patients were on the very verge of death—there is toxin present in the cultures that might produce such results as we have in the toxæmia of yellow fever without very large numbers of the bacteria being present. We have something similar in tetanus, and you know how hard it is to find the organism in this disease, yet it produces the deadly tetanus toxin. So I do not think we are prepared to throw this bacillus aside at present. We must continue to work with it and accept the final experimental results.

My recollection is, though I will not speak positively, that Dr. Reed has tried the Widal test on the colon bacillus with our serum, and does not get any such results.

With reference to Dr. Osler's question, I must say that I am not ready to accept Dr. Archinard's work as final, because the results reported are so much better than Sanarelli himself claimed. The young gentleman who made these experiments belongs to the army and is a very enthusiastic worker; but, so far as I know, he had no special training for the work, and whether his work is entirely reliable I do not know, but I want some additional experiments performed by independent workers before I will be willing to accept the results as regards the value of the Widal test with Sanarelli's bacillus in establishing the diagnosis of yellow fever.

OBSERVATIONS ON CARDIAC SYPHILIS.

By I. ADLER, M.D.,
of New York.

The majority of clinicians and practitioners are accustomed to consider syphilitic heart-lesions more or less as pathological rarities. On the other hand, a number of authors—Semola,[1] Sacharjin,[2] and others—have insisted on the frequency of cardiac syphilis, and have endeavored to establish certain diagnostic characteristics with a view toward its early recognition and prompt treatment.

Pathological anatomy has pointed out certain forms of heart-lesions as more or less characteristic of syphilis of the heart. Aside from those cases of so-called syphilitic endo- and pericarditis which, if at all connected with syphilis, are, as a rule, merely secondary to other primary lesions, we find the gumma, the interstitial or fibrous myocarditis and the syphilitic endarteritis, with their sequelæ, as the typical forms in which syphilis is manifested in the heart. These well-marked and typical lesions have been fairly well studied, though there are still numerous and interesting questions in the minute anatomy and pathology of these processes that require further investigation.

Within recent years Mracek[3] has published an extensive study of the whole subject, both from an anatomical and clinical point of view. It is, however, not always possible even for the pathologist to decide whether a fibrous myocarditis or a partial aneurism of the heart is due to syphilis or to other causes, so that even the anatomical diagnosis as regards syphilis is not infrequently doubtful.

[1] Ueber Herzsyphilis. Int. klin. Rundschau, 1892, Nos. 41 and 43.

[2] Die Lues des Herzens von der klinischen Seite betrachtet. Deutsches Archiv für die klin. Medicin, Band xlvi. p. 388.

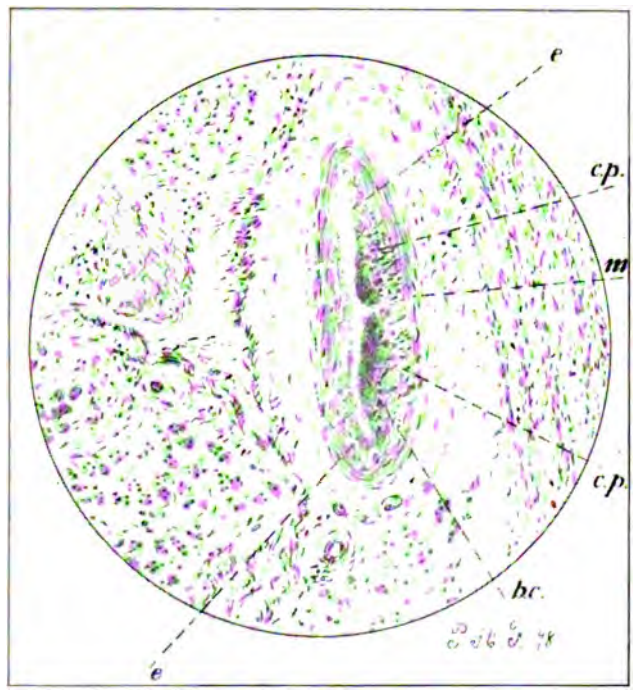
[3] Die Syphilis des Herzens bei erworbener und ererbter Lues. Archiv für Dermatologie und Syphilis, 1898, Band xxv. Supplementheft. This very excellent paper contains a fairly exhaustive review of the whole literature of the subject.

Thus the heart gumma, which is not found too often, remains after all the only unmistakable anatomical type of cardiac syphilis. Considering the relative rarity of typical gumma of the heart, and convinced that syphilis is much more frequently an etiological factor in heart disease than is commonly assumed, it appeared of some interest to examine a number of hearts of syphilitics not presenting any well-marked gross anatomical changes, with a view of ascertaining whether minute lesions could not be found sufficient to throw some light on the early development of luetic heart-lesions, and from which certain clinical deductions might possibly be derived.

It was thought best in the first place to examine the hearts of very young infants, not only because it might be interesting to study the behavior of congenital syphilis in reference to the heart, but principally because the possibility of confounding vascular and myocarditic lesions due to syphilis with those due to other causes (such as arterio-sclerosis, gout, alcohol, tobacco, etc.) was here reduced to a minimum. Four infantile hearts were thus examined. They were all from babies under four months of age that had exhibited unmistakable symptoms of syphilis: copper-colored skin eruptions, ozæna, fissures about lips and anus, mucous patches, etc. None had shown during life any symptoms of cardiac disease, and they all died during the summer and fall of 1897 of acute enteritis. The hearts and large vessels appeared to the naked eye entirely normal. The hearts were fixed in formaline, hardened in alcohol, divided into blocks of various size, imbedded in celloidine, and cut into sections, very frequently in unbroken series of several hundred. The sections were stained in various ways, but the ordinary hæmatoxylin-eosin stain was found most serviceable.

In two of these hearts a most careful scrutiny failed to discover any lesion ascribable to syphilis. Here and there minute hemorrhages were found, and in some places the smaller veins and capillaries were much distended. But throughout the coats of the vessels appeared perfectly normal, as did also the muscle-fibres and the interstitial tissue. The blood extravasations were quite fresh, and it is probable that they represented merely agonal symptoms. In the other two hearts, however, very characteristic though mostly quite minute lesions were found, lesions affecting the bloodvessels, the interstitial tissues, and the muscle.

PLATE I.



Infant two months old. Zeiss A. Oc. 3.

Small branch of left coronary artery, showing early stage of endarteritis.

e. Elastic membrane.
c.p. Cell-proliferation of intima.
m. Muscular coat.
b.c. Blood-clot in lumina of artery.

In the first of these hearts, from an infant about two months old, nothing abnormal could be detected except in one place in the outer wall of the left ventricle about half-way between the apex and the sulcus coronarius and near the pericardial surface, and here a small branch of the left coronary artery exhibited a very characteristic patch of endarteritis (Plate I.), the adventitia and muscular coat seem entirely normal, but on one side of the somewhat flattened vessel there is evident a very distinct proliferation of the intima. This proliferation takes place within and below the elastic membrane; it can readily be seen that the elastic membrane is lifted up, as it were, below and between its layers of elastic fibres. At first the elastica still covers the proliferating mass, though it gradually loses its undulating and looped appearance and becomes more or less straightened out. Following the course of the proliferation in serial sections through the little artery, we find the patch of new-formed cell material growing larger, bulging out more and more, and at its point of greatest development almost entirely occluding that part of the vessel's lumen, so that merely a very small slit remains open to the current. At this point, too, the elastic membrane has entirely lost its characteristic appearance, and can be traced only in threads and filaments of elastic fibres, irregularly distributed throughout the proliferating cellular mass. This latter consists of cells having clearly defined nuclei and finely granular very pale protoplasm. Owing no doubt to the pressure exercised upon them by the blood-current and the tension of the elastic vascular wall, these cells are all much flattened out and are packed together into layers, as it were, so that the nuclei appeared as if arranged with some sort of regularity. Probably for the same reason the individual cell-boundaries are not very distinct, the cells seeming to merge into each other, thus presenting in places the appearance as if the nuclei were dispersed throughout a rather amorphous finely granular substance.

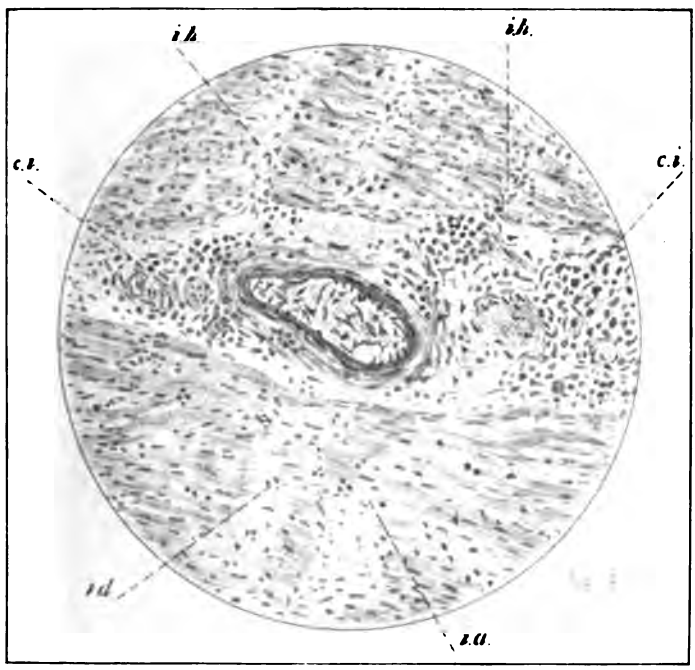
I will not enter here into a more detailed discussion of the minute histology and pathology of this form of endarteritis. It differs in some particulars from the description given by Heubner of endarteritis in the smaller arteries of the brain, but of its specific nature there appears no reason to doubt. There speak for this not only general considerations, the age of the subject, the possibility of excluding other forms of endarteritis, but more forcibly still the fact that in

the course of the systematic examination of the other hearts a fairly complete series could be established leading from this earliest form of endarteritis through various stages of development up to complete fibrous degeneration and total occlusion of the bloodvessels. In the immediate neighborhood of the diseased artery just described a very minute area was found in which the interstices between the bundles of muscular fibres appeared rather wider than normal and somewhat infiltrated with small cells. With the exception of this lesion just described nothing abnormal could be discovered throughout the entire heart, and it should be particularly stated that in the large vessels, aorta, pulmonary artery, and main trunks of the coronaries numerous sections failed to show any morbid alterations.

The fourth baby-heart exhibited more decided and extensive lesions. It was taken from a male child three and a half months old, which had died in October, 1897, with the symptoms of intestinal catarrh and broncho-pneumonia of left lung. As appears from the history, no signs of cardiac disease were noted during life. Macroscopically the heart appeared entirely normal, the valves were intact, the heart-muscles well contracted, somewhat anæmic, but uniform throughout. No degenerating patches to be made out anywhere, and the large vessels likewise appeared absolutely normal. Microscopical examination, however, demonstrated pathological conditions in their very incipiency indeed, but unmistakable. In the first place, endarteritis, as described above, was found in various vessels, both arteries and veins. In several places it was a smaller branch of the left coronary artery, situated immediately under the epicardium. In other places little vessels were affected that were located well within the heart-muscle itself, but in every instance rather nearer to the pericardial surface. The endarteritic process seemed more advanced than in the previous case, inasmuch as the entire intima was often involved, the proliferation being more bulky, thus more nearly obstructing the lumen of the vessels affected, and, moreover, in some of the vessels, just beginning to assume a more fibrous character, intercellular fibrous tissue making its appearance between the heaps of cells, which latter accordingly appear less numerous and set further apart from each other.

In addition to this endarteritic condition, perivascular processes could be observed. The perivascular space surrounding minute arteries and veins within the muscular tissue appeared broader than normal

PLATE II.

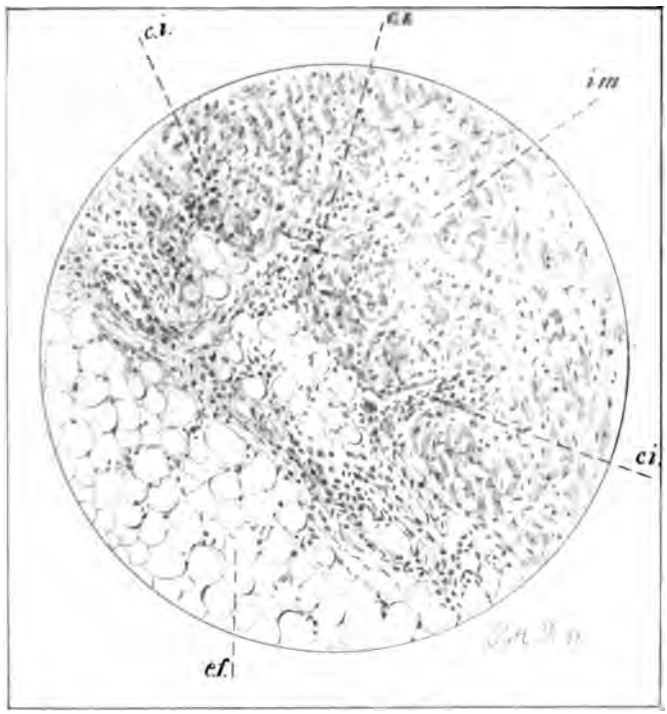


Infant three and one-half months old. Zeiss A. Oc. 3.

Left ventricle. Cell-infiltration filling perivascular space and radiating from there into the muscle of the heart's wall.

c.i. Cell-infiltration.
i.h. Interstitial hemorrhages between the muscle fibres.
i.d. Newly-formed connective tissue pushing apart the muscular fibres, which show beginning degeneration.

PLATE III.

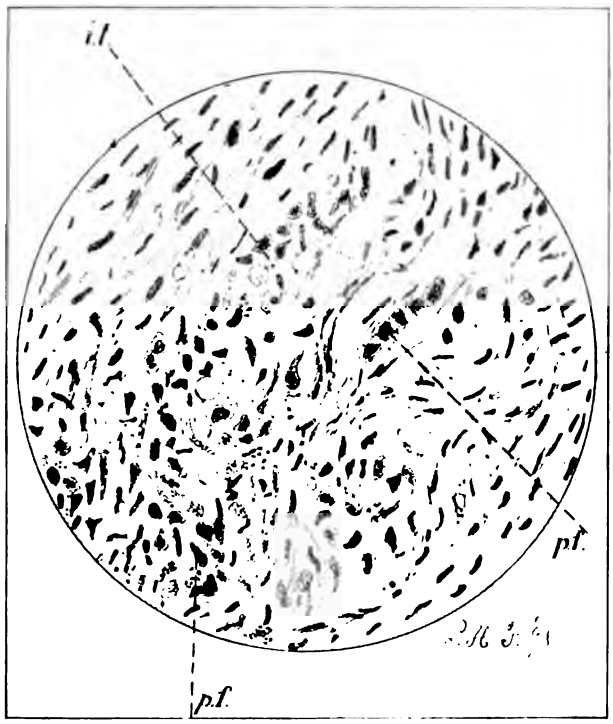


Infant three and one-half months old. Zeiss A. Oc. 3.

Left ventricle, showing epicardium and cell-infiltration in perivascular spaces, radiating from there into the muscular tissue.

c.i. Cell-infiltrations.
ef. Epicardial fat.
i.m. Interstitial fibrous tissue pushing apart the bundles of muscular fibres.

PLATE IV.

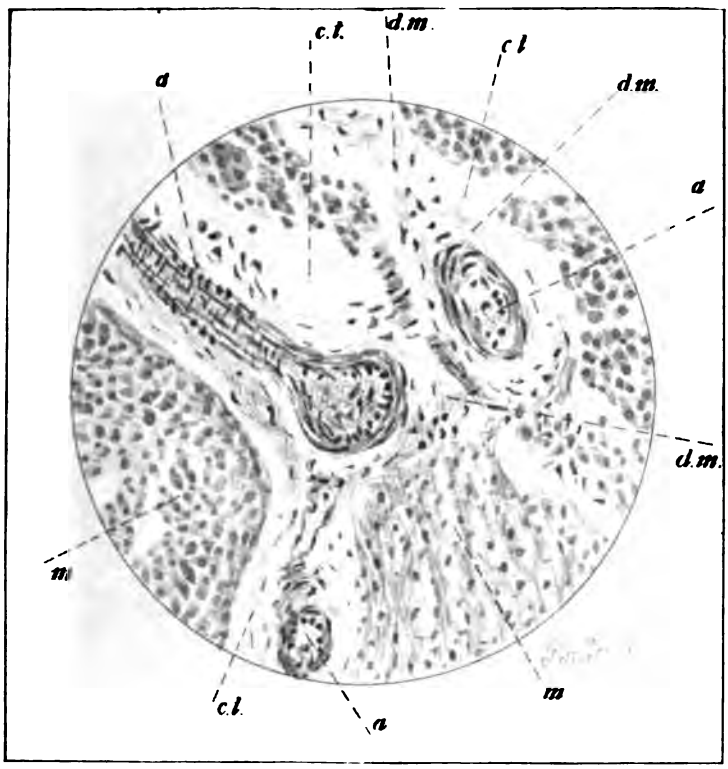


Infant three and one-half months old. Zeiss DD. Oc. 3.

Left ventricle, showing interstitial cellular proliferation and disruption of muscular bundles.

i.t. Newly-forming interstitial connective tissue.
p.f. Large epithelioid tissue-forming cells.

PLATE V.

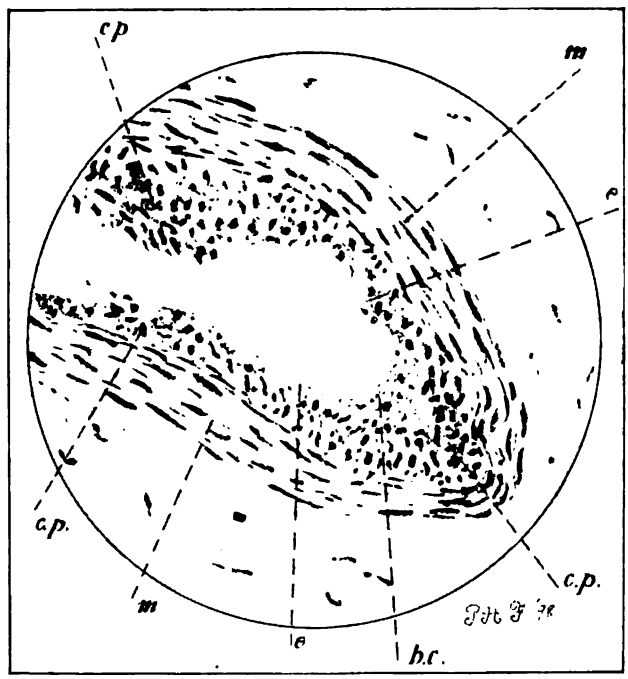


Infant three and one-half months old. Zeiss DD. Oc. 3.

Left ventricle, showing more advanced stage of interstitial connective-tissue formation.

a, a, a. Small arteries.
m, m. Muscular fibrils with enlargement of fibrous interspaces.
c.t. Broad area of fibrous tissue.
d.m. Remnants of muscle fibrils in state of degeneration.

PLATE VI.



Heart of infant three and one-half months old. Zeiss A. Oc. 3.

Left ventricle. Branch of coronary artery, showing proliferation of intima.

m, m. Muscular coat.
c.p. Cell-proliferation of intima.
e, e. Remnants of elastic membrane.
b.c. Blood-clot.

and more or less completely filled with leucocytes (Plate II.). From the perivascular space the leucocytes radiated out into the surrounding vascular tissue, invading the intermuscular spaces and forcing themselves between the striated fibrils. In another place the perivascular infiltration has lost its purely cellular character, and consists of very loose and soft connective tissue still rich in cells, while the muscular fibrils in the immediate neighborhood have become separated by wider bands of the same loose and wavy, partly cellular, partly fibrous material. Still in another place the connective tissue has become firm, more fibrous, and containing but very few cells. The muscular fibrils are now separated in all directions by comparatively broad areas of fibrous tissue, so that single fibrils or small bundles of fibrils appear dispersed amid a proportionately wide tract of fibrous tissue. Here and there, too, the nuclei of the muscular fibres have become pale and are stained but little by the hæmatoxylin. The transverse striation has become indistinct or has disappeared altogether, thus exhibiting the early signs of degeneration. All these morbid conditions appear only, it must be remembered, in minute microscopic patches, which are everywhere surrounded by entirely normal tissue. They are found scattered mainly through the walls of the left ventricle, principally near its pericardial surface, and to some extent in the interventricular septum. The walls of the right ventricle appeared normal. It should be added, too, that in several places perivascular infiltration and new formation of connective tissue can be demonstrated in the subserous layers of the epicardium of the left ventricle. It is evident that we have to deal here with the very early stages of interstitial myocarditis.

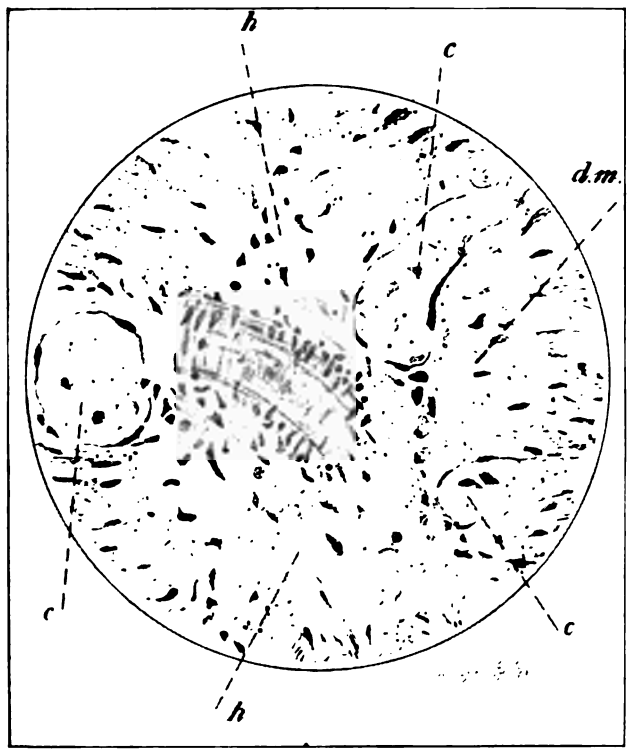
It may be confidently stated, therefore, that out of four hearts taken from syphilitic infants, two gave unmistakable evidence of disease traceable to syphilitic infection, although neither the clinical history nor the macroscopical examination at the autopsy pointed toward any heart lesion. It now became of interest to examine the adult heart under similar conditions, that is to say, the heart of adults who bore the unmistakable stigmata of syphilis, but who showed neither during life nor at the post-mortem examination any sign of cardiac lesion.

Through the courtesy of Dr. Schwyzer, I was placed in possession of two hearts, one male, one female, that fulfilled the required condition. Both patients had died of Addison's disease, caused by gum-

matous degeneration of the suprarenal cupsules, and had besides this other syphilitic lesions, more particularly interstitial hepatitis and gummata of liver. The one heart was taken from a woman thirty-seven years old. Pericardium and endocardium, including valves, normal. The heart muscle somewhat atrophic and flabby, showed layers of intense dark-brown pigmentation, some patches of atheromatous degeneration in the aorta and pulmonary as well as in the upper portion of the coronary artery. Microscopically similar conditions of interstitial myocarditis were found, as in the baby-hearts, though in a somewhat more advanced stage. The very early stage of mere cellular infiltration was nowhere to be met with. Areas of connective tissue containing comparatively few cells were seen to separate the muscle fibres, which very frequently showed signs of atrophy and degeneration. The smaller vessels, both arteries and veins, under the epicardium as well as in the substance of the muscle, were often the seat of endarteritis and periarteritis, the latter perhaps more frequent than the former. The endarteritic degeneration is in a more advanced stage than in the infant's heart. Vessels completely blocked were frequently seen, and the proliferation everywhere had assumed a decidedly fibrous character. Besides these processes, which are undoubtedly to be attributed to the syphilitic infection, there appeared numerous and rather large areas of muscular degeneration, the etiology of which is as yet not quite certain, but which do not seem to be directly dependent upon the syphilitic lesion. No connective tissue or cell infiltration appears between the muscle fibres, which latter retain their relative position and outline. They lose, however, their striation. The nuclei become at first indistinct, then disappear altogether. The entire mass takes the stain but imperfectly, and while, for a time, the single fibrils can still be made out, and no granules or droplets of fat are present, finally the fibrillary texture becomes indistinct and the tissue is converted into a pale, rather homogeneous colorless mass. It is difficult to decide whether this coagulation necrosis is due to the pathological condition of the vessels or in some way connected with Addison's disease and the abnormal and excessive deposit of pigment material.

The other heart was taken from a man aged thirty-eight years. There are no clinical symptoms of heart disease. The autopsy notes describe the heart as small, flabby, the muscle brown in color, inter-

PLATE VII.



Adult male heart. Zeiss DD. Oc. 3.

Left ventricle, showing interstitial hemorrhage.

c, c, c. Dilated capillaries.
h, h. Interstitial hemorrhage.
d.m. Degenerating muscular fibrils.

spersed with numerous minute gray streaks. No abnormal fatty deposit in or about the epicardium, and the valves normal. On microscopic examination interstitial myocarditis was found as described above, but in a still more advanced stage. The areas of firm connective tissue are larger and more extensive, the degeneration and destruction of muscular fibres have assumed larger proportions, so that these areas become visible even to the naked eye as minute gray streaks imbedded in the brown heart-wall. The vascular changes are equally well marked, but besides the endarteritis and periarteritis we find in this heart, in many places, enormous dilatation of the capillaries and small veins which are engorged with blood, and in addition thereto small hemorrhages, the extravasated blood occupying the perivascular spaces and pushing its way from thence between the muscular fibres forcing them apart and breaking them into fragments. As far as I can gather from the literature, Ehrlich[1] first described these hemorrhages in heart syphilis, his own case showing typical hemorrhagic infarction of the heart. Mracek has also described this condition in several of his cases. Both have had before them more advanced stages of the process than here described.

To complete the series, I have had the good fortune to obtain, through the kindness of Dr. Van Gieson, a heart taken from the body of a negro woman between thirty and forty years old, which showed macroscopically in a very exaggerated form all the typical lesions of cardiac syphilis. The aorta and pulmonary, as well as coronary artery, contained numerous patches of degeneration. In the left ventricle and in the interventricular septum there were several gummata, large areas of fibrous degeneration are distributed throughout the walls of both ventricles and septum, and fibrous patches were to be seen in the visceral pericardium, the papillary muscles and the trabecles. The endocardium was apparently normal. Microscopical examination, besides the typical structure of the gumma, revealed everywhere destruction of muscle and its replacement by fibrous tissue. The bloodvessels were degenerated, and scarcely a normal vessel was to be found. All stages of the process were represented. Some were hardly to be recognized as bloodvessels, and could be traced as such only by remnants of elastic fibres (orcein stain), others still partially

[1] Zeitschrift für klinische Medicin, Band 1, S. 378.

nt of origin of the disease, and the interstitial myocarditis and subquent degeneration and destruction of the muscular tissue as commentary to the primary vascular lesions. It has further been own that before any functional disturbances or gross anatomical anges become apparent, interstitial myocarditis and its sequelæ, the sorganization of muscular tissue, may have become firmly established. articular attention should be called in this connection to the comrative rapidity with which the simple cellular infiltration is converted ito fully organized, though at first loose and soft, connective tissue, which latter again is quickly transformed into dense and hard, fibrous naterial.

Aside from anatomical and pathological considerations, conclusions of some clinical value may perhaps be deduced from these observations. It is evident that while therapeutic measures may arrest the process of syphilitic disease and cause absorption of gumma and other cellular proliferations and degenerations, they are powerless against fully developed fibrous tissue. In many other organs the cicatrization caused by the shrinking fibrous tissue does not necessarily entail serious disturbance of function. It is in most instances, if not too extensive, readily compensated. In the case of the heart, however, the loss of muscular elements and their replacement by fibrous tissue signify permanent impairment of vital function. It has been shown above that the vascular, interstitial and muscular lesions may be well established, and may have advanced considerably on their insidious course of destruction long before clinical symptoms warn us of their presence. It is therefore fair to assume that when clinical symptoms do appear the anatomical process has already attained some magnitude.

It is imperative, therefore, to establish the correct diagnosis at as early a stage of the disease as at all possible. Unfortunately there are no distinctive diagnostic features which characterize the various forms of cardiac syphilis as distinguished from other forms of heart disease. By careful attention to anamnestic and physical details, however, it will not infrequently be possible, in individual cases, to make the diagnosis of luetic lesion, if not absolutely positive, at least, very probable. It is self-evident that in many forms of heart disease, as for example, the purely senile form, the valvular lesions basis and myocarditis following these, the fatty, the

alcohol, and the nicotine heart, syphilis can, as a rule, be excluded, though it is by no means impossible that even these forms, especially the two last named, may occasionally be complicated with syphilitic lesions. Myocarditis, on the other hand, especially when occurring in younger individuals, not clearly attributable to some other causation, should always give rise to a suspicion of syphilis. Active syphilitic lesions in other organs would, in such cases, go far toward corroborating the diagnosis, but even when no such lesions are to be found, the absence of any other satisfactory etiology would warrant the tentative assumption of syphilis, and this whether the patient gave a history of previous syphilitic infection or denied it.

In this respect the same principles that have for a long time been applied in the diagnosis and treatment of presumptive syphilis in other organs hold good for the heart as well. Here, as well as elsewhere, a diagnosis can often be established *ex juvantibus*, though it must be remembered, in view of the anatomical considerations set forth above, that the failure of antisyphilitic treatment to affect a cure does not necessarily miliate against the diagnosis. But it is not only the well-marked myocarditis that requires attention.

There are numerous cases, especially in younger individuals, of so-called weak or irritable heart associated either with bradycardia or more frequently with tachycardia, and always with more or less arrhythmia, that are often the result of syphilitic lesion.[1] In these cases there are none of the graver physical signs of cardiac disease. No murmur, no dilatation of the ventricles. The symptoms consist mainly of functional disturbances, and it is often difficult to differentiate between neurasthenic, hysterical, or incipient organic processes. Semola contends that arrhythmia and tachycardia, even without other functional disturbances not clearly to be accounted for on other grounds, and not readily yielding to the ordinary treatment with digitalis and other heart regulatives, are pathognomonic for cardiac syphilis, and he reports a number of such cases cured by iodides and mercury, after all other treatments had failed. It is impossible to decide at present to what extent Semola's views are borne out by actual fact. The clinical and anatomical material is as yet entirely insufficient for that purpose. I have observed several cases which

[1] Such cases have first been described by Fournier, Leçons sur la Syphilis, 1873, and by various authors after him.

correspond quite closely with those published by Semola and which were entirely unaffected by the usual methods of treatment. They recovered rapidly under mercury and iodide of potassium.

Bearing in mind the necessity for timely therapeutic intervention before the minute lesions in the heart-walls have assumed irreparable proportions, it may be as well in all such cases, even if the diagnosis is doubtful, to give the patient the benefit of the doubt and proceed without delay with energetic anti-syphilitic treatment.

Angina pectoris has frequently been mentioned in connection with cardiac syphilis. Hallopeau,[1] Rumpf,[2] Sacharjin, and others have described cases of angina pectoris of syphilitic origin. In some instances the angina was the sole symptom of disease, in others it was complicated by more or less grave myocarditic symptoms. Hallopeau and Rumpf appear to consider their cases as due to a syphilitic process affecting the nerves of the heart; commonly, however, angina pectoris is considered as in some way caused by endarteritis of the coronary arteries. We have seen that syphilitic endarteritis of the small branches of the coronary is always to be found in heart syphilis. Palma,[3] Crooke, Cockel,[4] and others have described endarteritis syphilitica of the larger branches and main trunks of the coronaries. It is, therefore, not surprising that syphilitic angina pectoris is occasionally met with.

The following case has come under my own observation:

Mr. H., aged fifty-three years, merchant, acquired initial sclerosis eight years ago, followed by moderate secondary symptoms. He was subjected to several courses of mercurial inunction, twice at Aix la Chapelle, in connection with sulphur baths, and took iodide of potassium off and on for years. Two years previous to his present malady his general health was much affected by reverses in business, though he never complained of any heart symptoms. He was first seen by Dr. Stieglitz, the family physician, on the evening of March 12, 1897. For some days previously the patient had complained of pain in the region of the heart and of general debility. On that evening, walking from his bed to the sofa, he was suddenly seized with an acute attack of intense pain in the left half of the chest, together with short and difficult respiration, great precordial oppression, palpitation of heart, and a feeling of impending death. He was seen by Dr. Stieglitz within fifteen

[1] Annales de Dermatologie et de Syphiligraphe, 1887, vol. viii. p. 747.
[2] Die Syphilitischen Erkranhungen des Nervensystems, p. 500, ff.
[3] Prager Medicinische Wochenschrift, 1882, No. 6.
[4] Schmidt's Jahrbuecher, 1893, Bd. 238.

minutes after the onset of the attack, which was then already beginning to subside. He had less pain and breathed with less difficulty. The pulse was irregular, thready, and rapid (100 to 115). Examination of the chest showed extension of the cardiac dulness about three centimetres beyond the left mamillary line. To the right the dulness did not extend much beyond the border of the sternum. The action of the heart was irregular, jerky, and tumultuous. The lips and finger-nails were cyanotic, hands and forehead clammy. Under the influence of morphine, strychnine, and nitro-glycerine the distress disappeared, the acute attack subsided and the heart's action slightly improved.

I saw the patient with Dr. Stieglitz on March 13th. He was extremely weak, hardly able to move, somewhat cyanotic, extremities cold and clammy. The pulse was very irregular, easily compressible, thready, and rapid, varying between 100 and 130, the slightest exertion increasing the number of beats considerably. There were no signs of arterio sclerosis. The apex-beat neither visible nor palpable. The heart, especially the left ventricle, dilated. The dilatation was demonstrably increased by any exertion such as turning in bed or coughing. He complained of pains in the left arm from the shoulder down the entire length of the arm, and of a sensation of numbness in the finger-tips. The main nerve-trunks of the left arm were very sensitive to pressure, but no anæsthesia could be made out. The centre of the manubrium sterni, at about the level of the second rib, was extremely sensitive to touch and the seat of considerable spontaneous pain. A similar spot, though not quite so tender, was located in the body of the sternum at about the level of the mammilla. On the left leg the traces of former serpiginous ulcerations could be seen. With absolute quiet in bed, ice-bag to region of heart, strophanthus, morphine, and moderate doses of iodide of potassium, the patient improved but slightly, the pulse became slower, not quite so irregular, the dilatation of heart receded a little, pain in arms and sternum continued unchanged. He still reacted upon the slightest exertion with palpitation and dyspnœa, and the general prostration and debility persisted.

On March 21st he had, without known cause, another attack similar to the first, though not quite as severe. I saw the patient for the second time on March 22d. His condition was but little better than on my first visit, though the heart was not quite as much dilated and the pulse somewhat stronger. Besides the tender spot in the sternum, a very sensitive area could be made out on the sixth rib a little beyond the mammillary line in the right half of the chest. Here the rib was thickened, extremely sensitive to pressure, and on auscultation a distinct friction sound was noted over this spot. The concussion of the liver, which latter was not enlarged nor sensitive to the touch, was distinctly painful. The doses of iodide of potassium were now increased and mercurial inunctions systematically instituted. Gradual improvement set in.

Early in April very suddenly there began attacks of hiccough, which lasted throughout the next seven days for many hours at a time, and proved most

distressing and debilitating. Numerous external and internal remedies were tried, but failed to give any relief. The only measure that almost instantly stopped the singultus was a rhythmical traction upon the tongue, the patient at the same time making a deep inspiration. This procedure, however, was extremely painful, and while it cut short the attack did not prevent its speedy recurrence. Gradually, however, the attacks of singultus became shorter in duration and less frequent, and finally ceased altogether.

Under the influence of continued mercurial inunctions and large doses of iodide of potassium the patient now improved rapidly. No more attacks of angina and acute dilatation recurred. The heart rhythm became regular, the pulse fuller and stronger. The painful spots in the sternum, rib, and arm disappeared entirely. By the end of April the patient was able to sit up and walk about his room, and on May 8th he was able to go out for a walk. Since that time he has resumed his usual occupation and habits. He has remained subject, however, to attacks of palpitation, though without any pains, and on several occasions after some over-exertion he has had slight attacks of heart weakness with some dilatation of left ventricle.

It is evident that we have here a case of myocarditis with acute dilatation of heart and angina pectoris. There can be no doubt that the disease was of syphilitic origin. The absence of any arterio-sclerotic symptoms, the simultaneous outbreak of fresh syphilitic lesions in sternum, ribs, and nerves, the failure of digitalis and other heart-tonics to influence the condition, and the rapid and decided effect of the antisyphilitic treatment concur in corroborating this. It is worthy of note, too, that even larger doses of iodide of potassium seemed to have no effect, and the improvement commenced with the systematic use of mercurial inunctions. Until within a few days of the severe and acute outbreak the man had apparently been well and had never experienced any heart-symptoms. But, nevertheless, and notwithstanding the occasional courses of inunctions and iodide in previous years, the myocarditic process had undoubtedly for a long time been slowly developing, though causing no symptoms until changes in the vessels and heart-muscles had been effected sufficient to produce this sudden break-down of the cardiac functions.

Reviewing, in conclusion, all these anatomical and clinical considerations, the necessity becomes apparent of methodically considering syphilis as an etiological factor in heart disease. It may not happen very often that an absolutely positive diagnosis of heart syphilis can be established, but in every case in which the etiology is not absolutely clear, and in which syphilis cannot with reasonable cer-

tainty be excluded, the iodides and mercurial preparations should be accorded the same privileges as the digitalis and strophanthns, strychnine and nitro-glycerine. If carefully administered they cannot do any more harm than these latter, and may do immeasurably more good.

I desire to take this opportunity to express my indebtedness to Dr. Van Gieson, Dr. Schwyzer, Dr. Maisch, and the staff of the Foundling Asylum, especially Dr. Norton and Dr. Northrup for the courtesy and kindness with which they furnished me with valuable material for this investigation.

TWO ATTACKS OF TEMPORARY HEMIPLEGIA OCCURRING IN THE SAME INDIVIDUAL AS THE RESULT OF THE USE OF PEROXIDE OF HYDROGEN IN A SACCULATED EMPYEMA (PLEURAL).

By E. G. JANEWAY, M.D.,
OF NEW YORK.

The following history of the development of two attacks of hemiplegia of temporary duration as the result of the use of peroxide of hydrogen in the sac of an empyema will, I trust, prove of interest as well as serve as warning:

Mr. B., forty-one years of age, a right-handed writer, was referred to me by Dr. Axtelle, of Waterbury, Conn. Two years previously he had developed a pleurisy on the left side, which had been aspirated. One and one-half years after this event a swelling developed in the left lumbar region, which bulged when he coughed. This Dr. Axtelle had incised four months preceding his visit to me, and found that it communicated with a sacculated empyema at the base of the left lung. After this the patient had used peroxide of hydrogen to irrigate the sac. On November 25th, three and a half months after the operation, two minutes after the injection of a wineglassful of the peroxide, as he noticed it to bubble inside, he felt very queer and, according to his wife, became unconscious for a second, and of a pale-greenish color. Immediately he found that his right arm and leg were numb and powerless. He did not lose the power of speech. This loss of power of the right arm, which was complete, and of the right leg, which was almost so, lasted for twenty-five minutes, and then passed away completely. After this he described himself as having felt as well as ever, except that he had been frightened by the occurrence.

Three days after this first attack he had an exactly similar seizure, except that he lost power in his neck also, his head dropped, and he had difficulty in breathing. The paralysis of the right arm and leg was again complete, and lasted as before—twenty-five minutes. On questioning, the fact was elicited that the sinus had so far closed that no air or fluid escaped after the introduction of the peroxide.

I examined Mr. B. sixteen days after the first of these spells. He then presented the healing incision and sinus in the left lumbar region. The physical signs on the left side were few and only to be made out by careful examination. There was some dulness in the lower part of the thorax; on auscultation the respiratory murmur was feebler than on the right side. Only by the ear could adventitious sounds be heard over the above-described area near the vertebral column. Neither with the binaural stethoscope nor with the phonendoscope could they be elicited. These consisted in rather large liquid râles occurring during the act of coughing or during an inspiration following several short acts of coughing.

This is an illustration, to digress for a moment, of the fact of not infrequent occurrence, that those who trust alone to auscultation by means of stethoscopes are liable to overlook or miss those indications of disease which are produced beneath the layer of normal, or nearly normal, lung tissue. On many occasions I have been able to detect a central pneumonia earlier by immediate than by mediate auscultation.

But to return to the thread of our story. At the time of the second examination, six days after the first, these phenomena had disappeared; only the slight dulness and the feeble respiratory murmur remained. On the occasion of this second visit the patient said that the discharge had ceased, and he felt that there was no accumulation within.

In this connection it may be of interest to recall to the members the case published by Leudet. This will be found with other cases of nervous phenomena developed in the course of an empyema, or more especially of lavage, of the sac of an empyema, in the work of L. Bonveret on empyema, published at Paris in 1888. He has collected a series of cases which he has grouped under the head of embolic, slow paralytic, syncopal, and convulsive, following empyema, or more especially lavage of the sac, or the introduction of a tube in the sinus. This and the following are similar in most respects to the one whose history I have detailed.

Briefly, the facts of this case were: that a young man, twenty-one years of age, had a pleurisy of the left side, filling the pleural sac in ten days. At the end of a week two litres of serum were removed by thoracocentesis. Three days later a pleuro-bronchial fistula gave exit to a great quantity of pus. Four days after this a new thoracocentesis gave exit to a litre of cloudy and opaque liquid. At the end of four months an incision into the pleura was made and the sac was regularly washed with a solution of iodine. Gradually the sac diminished, and on several occasions it was necessary to dilate the fistulous tract. Thirteen months after the operation for empyema,

whilst his mother, as she had been accustomed for a long time, washed the sac with a solution of iodine, having first introduced a new tube for one which had long remained in the fistula, the young man was suddenly seized with a general malaise, a sensation of numbness in the right side of the body, and an impossibility of speaking. The consciousness was not lost, and there was no convulsive movement. He knew that he could neither move a finger nor limb of the right side. Gradually the power of motion returned. Two months later a similar attack, though lighter, occurred. A third happened when the physician was himself washing out the cavity, which had become so retracted that it would hardly hold two-thirds of a wineglass of liquid. The physician essayed to measure the size of the sac by pouring in water. A resistance was experienced, and the tube was pushed out by the liquid. The patient rose, staggered, and his speech became embarrassed. He was placed in a horizontal position, with a pale face, the right hand and leg paralyzed, without power of speech. After fifteen minutes the speech returned, and a few moments later the power of movement of the right side. After this irrigations were continued for a year without further nervous accident.

So also this case, which was reported by Dr. L. Forgues, surgeon in the French Army, in the *Archives de Médécine et pharmacie Militaires*, Paris, 1894, vol. xxiv., has somewhat similar features:

A soldier, twenty-two years of age, was admitted to the hospital, December 5, 1891, with broncho-pneumonia. Seven weeks later the beginning of pleurisy is noted, and twenty days afterward 700 grammes of pus were removed by aspiration. The operation for empyema of the left side after two days gave exit to 1300 grammes of pus. Daily lavage of the sac was performed at first, but afterward according to the requirements of the case. About three months after the operation, during the giving of a lavage, the surgeon being engaged in retaining the drainage-tube, which was very short and had given pain by pressure on the border of the wound, the patient suddenly lost consciousness, having a pale face, a cadaveric look, largely open eyes, and dilated pupils. The heart-beat and the respiration were suspended and the general sensibility was abolished. No convulsions nor contractions occurred. After the use of cold flaggellation the heart's action and the respiration returned in about a minute. The patient had a vague expression for some moments, then recognized people around him, but had no knowledge of what had occurred. Four or five minutes later it was found that the right arm and leg were paralyzed. After twenty-five minutes power returned in the right leg, but it was three hours before the right arm could be used. Lavage was abandoned after this. On two occasions in the subsequent history the fistulous tract closed, but owing to accumulation of pus in the sac had to be reopened. The man finally recovered without another paralytic attack. In this case, as in the one which I have brought to your notice, though the hemiplegia was on the right side, there was no aphasia.

For attacks such as the three to which your attention has been drawn the most natural explanation would be to suppose that something had passed into the circulation and had produced an anæmia of the left side of the brain, or, more properly speaking, of a portion of this area. If we extend the study, however, and include those cases in which convulsions have also occurred, these have in certain cases been considered to be dependent on embolism, but a difficulty has been encountered in the cases which terminated fatally, and after careful search no satisfactory evidence of embolism has been found at the autopsy.

So far as a rather hasty examination of the literature is concerned, the three cases here recited are the only ones obtainable in which collapse and temporary hemiplegia have been the sole phenomena. In view of the fact above mentioned, that embolism could not be proven, the theory has been advanced that such seizures as had collapsed with subsequent convulsive attacks—the pleuritic epilepsy of some writers—could best be explained by invoking reflex action, and by supposing that a contraction of the cerebral arteries or an inhibition or excitation of the cerebral cortex was the occasion of the untoward nervous phenomena, with the additional explanation that in cases in which paralysis existed afterward that hemorrhages had occurred. But such explanation will not avail for the three cases here narrated, hemiplegia following or, more rightly, associated with collapse. It is a little singular that in these three cases, all with right hemiplegia, only one had aphasia. Hence, under the reflex theory, a narrower area of arterial spasm or cerebral inhibition must have been involved in two cases than in the case of Leudet. The idea which has been formulated that intoxication is responsible for such conditions would not be tenable so far as peroxide is concerned, nor does a study of the others enable one to be satisfied with such a theory.

To my mind, the phenomena are best explained by supposing the hemiplegia to be due to an embolism, but of such a nature as to soon disappear. The only substance capable of thus acting would be either air or gas. In the case which I have narrated, as in the others, the attack has occurred when the conditions were such as to produce some pressure within the sac; by liberation of oxygen from peroxide in this case; by measuring size of sac, Leudet once; by change of tube with lavage, Leudet once, and case of Dr. Forgues, of pressure to hold tube

in place with lavage. The question which has occurred to me is, Do not the events point toward the possibility that under the conditions air or gas may have found entrance into the radicals of the pulmonary veins through stretched or torn granulation tissue helped by a forcible inspiration at the time of the accident. Air embolism barely possible, oxygen embolism may be the solution which we seek to explain these cases. Oxygen could only be the agent when peroxide had been used, as in the case recorded. It can, of course, be objected that air, and more particularly oxygen, would either be rapidly absorbed or else kill by its accumulation in the heart. We are, however, concerned in these cases about too small an amount to bring about the latter result. It may be well to remind the adherents of the reflex theory that in the case recorded by Leudet the lavage was continued for a year after the last attack without recurrence. We may well ask what has become of the sensitive nerve so susceptible in provoking reflex.

As regards collapse alone, it is possible that it can be produced as the result of a reflex influence. It seems to me that a careful examination of the history of certain of the convulsive cases, especially those followed by, or rather associated with, hemiplegia, or paralysis, strongly suggest something sent by the circulation to the brain, possibly some of the injection fluid or pleural contents by the aspiration influence, causing capillary embolism.

Shortly after meeting this case I found an article by Prof. Lewin in the fortieth volume of the *Archiv für experimental Pathologie und Pharmacologie*, entitled, "About the Penetration of Air from the Bladder into the Heart and the Path of its Passage."

Prof. Lewin, in this article, describes experiments on animals in which death was produced by injecting air into the urinary bladder, thus producing air emboli. The air entered the venous system through the pelvis of the kidney, and was observed in the vena cava and aorta by means of a laparotomy previously performed. The air could also be heard to enter the renal vein and be made out in the heart during its continued activity following the death of the animal. Prof. Lewin thinks that the air penetrates preferably by the lymphatics into the vein by preformed paths, not necessarily through torn openings.

Such a case is suggestive in connection with the theory which has occupied us.

DISCUSSION.

DR. HENRY HUN: That all of these cases of paralysis after the use of peroxide of hydrogen cannot be due to air embolism appears from a case which I saw about a month ago, of a young man with a sinus above Poupart's ligament, the abscess coming on some months after a severe blow upon the back, and, so far as probing would show, seemed to be due to caries of the vertebræ. Some six weeks before I saw the patient his physician had injected a half ounce of peroxide of hydrogen without any ill effect. Five or six days after this first attempt, however, he did the same again; but this injection did not escape freely, and immediately the patient complained of severe pain in his hips, and both legs became paralyzed and remained so for some three hours, and even after six weeks he did not walk as well as he had done previously. In this case, as in those of Dr. Janeway, there was the probability of pressure, the peroxide not escaping freely, and it is possible, in my case, that there might have been an opening through a carious vertebra into the spinal canal, and the pressure might have acted directly upon the cord. It was, however, a temporary paralysis and evidently not of embolic origin.

DR. FITZ: It seems to me the theory most in harmony with the condition is that advanced by Dr. Janeway, though negative results post-mortem will hardly hold, because so slight. In case of the theory of air embolism, and against that view are the cases of pneumothorax, for if it is correct, more accidents would be expected to occur in connection with this condition.

DR. JANEWAY: The points of interest are the fact that the pleurisy was on the left side and the paralysis in all three cases on the right side. That would infer, if we were going to have spinal reflexes, that the action was on the other side of the cord, in which case we could not have aphasia. As regards pneumothorax, most of these accidents happened when the sac became very small, when we could have granulation tissue, that if broken, air might be forced by aspiration into the circulation. If you look over the history of the convulsive cases, not infrequently it will be seen that some blood was found at the next washing. I only offer this as a theory, and do not feel that any one can be sure, but it hardly seemed to me that the reflex theory would hold in these cases.

ANTITOXIN TREATMENT OF PNEUMONIA.

By ANDREW H. SMITH, M.D.,
OF NEW YORK.

It is extremely probable that the pneumonic process as we see it from the moment of invasion to the crisis implies infection by the agency of a continually changing set of microbes. Welch has shown that the virulence of the coccus is inversely as its age, the organisms taken from the centre of a pneumonic focus having very little potency, while on the edge of a patch which is still spreading they are most active. The inference to be drawn from this, and which is also supported by the behavior of artificial cultures, is that the infection of the system is not maintained through the whole period of pyrexia by the same microbes, but by a constant succession of cocci, the older ones becoming inert, and fresh ones carrying on the work of supplying the toxin. This supply fails soon after the local process has ceased to spread, simply because there are no longer any young bacilli to maintain it. But while it would seem as if this might afford a sufficient explanation of the phenomena of defervescence by crisis, yet the observations of the Klemperers and of subsequent investigators make it reasonably certain that there is an antitoxin produced that has its share in the result.

We are apt to think of the process of absorption by which resolution is ultimately effected as beginning *after* the crisis, whereas it is in operation from the first moment of the disease, as is shown by the early infection of the general system which it brings about. Up to the point of consolidation the rate of deposition is far greater than that of removal, and a rapid accumulation of exudate takes place in the air-cells. This exudate, however, is not permanent in constitu-

tion. It immediately begins a process of change, and, as we have seen, the organisms contained in it change their properties also. As time goes on there comes a period when the deposition of fresh infective material is less active than the absorption of that which is older. At this point an antitoxic effect becomes apparent, and in the cases terminating by crisis a rapid fall of temperature takes place. In the cases terminating by lysis, either the deposition of fresh material is protracted by the invasion of new territory or the absorption of the older material is for some reason less active.

As early as 1888 Netter rendered mice and rabbits immune to pneumonia by injecting them with fluid prepared from the dried spleen of infected animals. Subsequently he employed an old pleuritic exudate containing pneumococci, and at last the sputum of a pneumonic patient which had ceased to be virulent after the crisis.[1]

Pursuing this line of investigation, Foa found that the injection of an attenuated culture of the diplococcus of pneumonia into an animal gave immunity against the disease for several months. He produced the injection serum by precipitating with ammonium sulphate the culture-broth containing the diplococci, and filtering repeatedly. The filtrate was injected into the veins of rabbits daily for three or four days. Again, he made an extract of the muscles and viscera of a rabbit dead from pneumonia, precipitated it in the same way and got the same immunity. The extract from a healthy rabbit, when injected, gave no immunity.

He then studied the immune animal, drawing the blood and taking the serum after coagulation to inject another animal, which also became immune. As a control experiment he injected a rabbit with blood of a man dead of pneumonia; death resulted. He states that several species of virus are formed, one seeming to act on the nervous system, another on the blood and tissues.

The Klemperer brothers verified these results.[2] Their report is briefly as follows: Two rabbits were injected each with 20 cm. of pleuritic exudate taken from a pneumonic patient, and which by culture was shown to be free from living bacteria. Fourteen days later both were inoculated with a virulent culture. Both survived, while the control animal died. Later they immunized animals with pneu-

[1] Centralblatt f. klinische Med., 1888, ix. No. 15.
[2] Berliner klin. Wochenschrift, August 24 and 31, 1891.

monic sputum taken before the crisis and heated so as to destroy the poison. The same result was obtained by heating to 60° C. a glycerin extract of pneumococci. The bacteria were washed from agar cultures with sterilized glycerin, which was exposed to heat for one or two hours and filtered repeatedly. They found that immunity resulted from doses proportioned in quantity to the strength of the preparation. It was employed subcutaneously.

They found, further, that dogs can be immunized against pneumonia, and can also be cured of the disease. This cure takes place through the serum of immune animals immunized by taking in the products of the activity of the pneumococcus. This immunizing serum does not cure by killing the cocci in the system, for after four days' contact with the serum the bacteria injected into an animal caused death. In fact, the bacteria in contact with this serum increase in number. At the same time the serum, if injected, prevents the formation of the poison in the body of the animal. This may be explained in one of two ways—either the serum hinders their power of forming poison, or the cocci go on forming poison, and the serum counteracts its effects, or, through chemical changes, renders it inert. At any rate, the cocci become harmless in the animal, their evil influence being destroyed by the reaction of the body cells, especially the white blood-corpuscles.

If pneumotoxin and curative serum be mixed and injected into an animal, there is no rise of temperature and no effect from the poison, while toxin alone kills the animal, with symptoms of septicæmia.

They next inquired whether the pneumonia cured in animals by the serum is identical with pneumonia in man. Their autopsies in animals dead of pneumotoxin injections did not show the fibrinous exudation in the lungs characteristic of pneumonia, but diplococci were found in the blood. However, it is not the pneumococci themselves, but the poison that they produce that gives the septicæmic symptoms. This poison, when formed at the seat of injection, reaches the blood sooner than the cocci themselves. Also, if we filter out the cocci, the poison remaining in solution kills the animal injected as effectually as the original culture.

As compared with animals, man is only slightly susceptible to the pneumococcus. Living cocci can exist on healthy mucous membranes without doing harm, and are found in the sputum of healthy

men. If we inject men subcutaneously what results do we get? The Klemperers experimented by injecting themselves, and found that no reaction resulted from small amounts; from larger ones a local swelling, with rise of temperature and febrile symptoms, resulted, passing away in a few days. Hence, they conclude that men are much less susceptible than dogs to the same relative doses.

They conclude that in man it is not the exudation in the lung that renders the disease so grave, but the general infection from absorption of the bacterial poisons in the exudate into the circulation, acting on the heart and vital centres, and producing febrile symptoms. In animals injected the poison enters the blood-stream directly and produces fever at once. The poison increases for some days, and then antitoxin is produced and immunity results. Serum taken from pneumonic patients after the crisis is found to cure pneumonia in dogs. They conclude that from pneumotoxin in man is produced antitoxin at the time of the crisis, and this counteracts the effects of the toxins. Thus the so-called crisis in man is the beginning of the formation of the antitoxin, and though the cocci remain for some time in the blood they are no longer harmful.[1]

They then question whether immunity in man results after the crisis, and conclude, from researches and experiments, that it does occur, but is only temporary.

With regard to the treatment of pneumonia, they say at present we use supportive measures, awaiting the formation of antitoxin. But the aged and the weak succumb. They suggest that by using the immunizing serum from animals we may hasten this process and save lives. They have treated some cases in this way with apparent benefit, as shown by fall of temperature and slowing of pulse and respiration. But not enough have as yet been treated to arrive at a definite and final conclusion as to the value of the treatment.

An important discussion on this subject took place at the Academy of Medicine in Turin, December 2, 1892.[2]

Lara, chief physician of the Hospital of San Giovanni, reported the results of ten cases of pneumonia under serum treatment. Five of these cases were double, five single. Eight of the patients were young

[1] This statement is not in accord with more recent observations, which show that cases in which cocci are formed in the blood generally prove fatal.

[2] Journ. de Médicine, 1893.

persons, two advanced in years; six were robust, four of debilitated habit. The serum was in some cases from immunized rabbits, in other cases from dogs, and in still other cases a glycerin extract was employed made from the viscera of refractory animals. In no case was there any local reaction. The glycerin extract produced no observable general symptoms. Serum from dogs caused nervous excitement; that from rabbits produced general agitation and a temporary aggravation of the disease.

In all but three cases there was reduction of temperature, not sudden, but after an interval.

A change in the character of the pulse was observed, without a reduction in the number of beats.

There was no immediate change in the respiration, but after a time it became somewhat slower.

The crisis took place in three to five days. The convalescence was rapid and complete; complications were rare and of little gravity. The reporter considered the results encouraging.

Bozzolo reported five cases treated with serum from rabbits prepared by a special process not described. There was rapid fall of temperature in every instance. Four of the patients recovered and one died after defervescence. The kidneys were unaffected.

De Renzi reported that during the past year he had treated ten cases of pneumonia with anti-pneumonococcic serum prepared as follows:

The animals were inoculated with a non-lethal quantity of pneumonia virus, the dose of which is gradually increased until a strong immunity is produced. Serum from these animals was injected into the patient. Only severe cases were selected for treatment. In every case cure resulted. In one case the temperature came down on the third day, although there were signs of diffuse hepatization. Of five other cases admitted during the year and not treated with serum, one died. Although the author admits that his cases might have recovered without the serum treatment, he considers his results decidedly encouraging as pointing to a real and efficient treatment of pneumonia.[1]

Wiesbecker[2] reports five cases of pneumonia treated with injections

[1] British Med. and Surg. Journal, March 28, 1896.

[2] Zeitschr. f. klin. Med., 1897, xxxii. p. 188.

of serum obtained from patients recovering from the disease. While there was no uniformity in the results as far as the objective signs are concerned, these becoming more and more severe in some cases after the injection, while in others the severity abated, there was in every instance a most remarkable improvement in the subjective conditions. This improvement was almost instantaneous, in one case being manifest within one and one-half minutes after the injection. But for one instance, in which the patient was a child only three years of age, we should be inclined to refer these marvellous results to suggestion, especially as they did not conform to the physical conditions present at the moment. Difficulty of breathing, pleuritic pain, malaise of every description disappeared as if by magic; recovery took place in every case, though not always with remarkable promptness. The quantity of serum in each case was 10 c.c.

Similar to this was the experience of Fourriere[1] in a single case treated by injections of goat's blood. The patient, a person past middle age, was recalled to life from an unconscious, fairly moribund condition, and, though death occurred after several days, there was an interval during which danger seemed to be over and recovery assured.

In 1897 Washburn, of Guy's Hospital, published his researches on anti-pneumococcic serum. His method was essentially that employed in producing diphtheria antitoxin. A pony was the animal selected, and after nine months' treatment, first with living and then with dead cultivations, the serum was found to possess marked protective powers. By using a special method of cultivation, it was found possible to maintain the virulence of the pneumococcus at a given level for a period of sixty-six days. This process is described in detail in the *Journal of Pathology and Bacteriology* for January, 1898. To maintain the virulence of this culture it must be kept in an incubator at a temperature of 37.5° Centigrade. He claims that under these conditions the anti-pneumotoxin can be accurately standardized.[2]

Several cases of pneumonia have been treated by Washburn and others with this serum. While its influence cannot be distinctly traced, it could fairly be considered to have contributed to the favorable result in some extremely unpromising cases.

[1] Journ. de Médecine, Jan. 1, 1893.

[2] British Med. Journal, 1897, i. p. 11.

We cannot avoid the conclusion, from this résumé of the achievements of serotherapy in its application to pneumonia, that up to the present time they can scarcely be said to amount to more than an encouragement to further effort. No really decisive results have been attained. In some cases the effect seems to have been favorable; but in view of the variable course of pneumonia under all forms of treatment, it is impossible to assign to the injections any positive share in the result. It can be only by the accumulation of a large number of observations that a conclusion as to the value of the treatment can be arrived at, and, unfortunately, the difficulties in the way of extended observation are such as to deter most investigators from pursuing the subject.

The first difficulty is found in the short life of the pneumococcus and its feeble power of resistance. Cocci that are virulent at the beginning of an investigation cease to be so as the investigation proceeds. On the other hand, toxins that are expected to produce only a moderate reaction when injected sometimes display an unlooked-for virulence. Animals apparently progressing normally toward immunity most unexpectedly succumb to septicæmia from a dose of toxin supposed to be entirely within the limits of safety. Again, animals that were readily immunized at first lose their immunity in spite of renewed inoculations, and the serum obtained from them ceases to be reliable. This variation in the conditions under which experimentation is conducted is liable to vitiate the most carefully drawn conclusions. If this be true under the favorable circumstances of the laboratory, what must it be in the exigencies of ordinary practice! If before employing a therapeutic agent we must resort each time to experiment to test the value of the specimen in hand, the usefulness of the agent will be very limited.

It is to be hoped that this difficulty has been overcome by Washburn's method, already mentioned, and that it will be possible in the future to command a supply of reliable antitoxin for the treatment of pneumonia, as we already do for the treatment of diphtheria. Efforts to produce such a supply are now being made by the Health Board of New York. Should they be successful, the value of the method will soon be determined.

DISCUSSION.

DR. V. C. VAUGHAN: This is a subject in which I am interested and in which I have done some work myself. I read a paper before the International Congress of Hygiene, at Buda Pest, on this subject. In a late paper by Loewy and Richter you will find a very complete review of the literature upon this subject. As Dr. Welch says, there is no evidence that there is a toxin and no evidence that anybody has ever produced an antitoxin for pneumonia. Every one who has experimented much in this line has come to the same conclusion. We find out the minimum fatal quantity of a culture that will kill a rabbit, and by injections of leucotactic substances we find that we can protect the animal temporarily against that small amount of the culture, but as soon as we double or treble the quantity of the germ we fail to protect the animal, no matter how much of the leucotactic substance we may use. I failed in all my experiments to get immunity.

DR. C. G. STOCKTON: There is a feeling, I believe, that the degree of leucocytosis has something to do with the somewhat abrupt decline usually seen in lobar pneumonia, and it has been stated, I believe, that the crisis depends upon the degree of leucocytosis in any given case. I have had during the past winter a very striking case, and if you will permit me I will pass around the temperature-chart and relate a few facts concerning these rather irregular curves and their apparent relation to the condition of the blood.

This patient was a child eight years of age. She had a relapsing lobar pneumonia, having had three distinct attacks within a period of eight weeks. There was no doubt in my mind about the nature of the disease, although there was at no time any expectoration. There were the classical physical signs of lobar pneumonia. The point that seemed to me of special interest, aside from the repeated relapses, is that the blood was found, during and just at the end of the attack, to be very low in cellular elements, including the white blood-cells. After the first attack there were 4000, after the second, which was less severe than the preceding one, the number had risen somewhat (about 6000), and an examination made at the end of the third attack (which was still milder) showed a greater prominence of the lymphocytes, the white cells were rising in number, and had reached about 10,000. There was nothing else peculiar about the blood except an increase of the eosinophiles and paleness of the reds. The temperature was taken regularly by a trained nurse, and an examination of the blood made five or six days after the end of the last attack showed it to be normal and to have attained a proper proportion between the lymphocytes and the polynuclear form of white cells. This case was to me unusual, and it seemed that it might bear this interpretation, that, in the absence of the normal number of leucocytes, particularly in the absence of a proper proportion between the multinuclear

form and the lymph cells, it might be said that the child did not reach the immunity that the ordinary attack of pneumonia would produce. That this has a certain amount of proof seems to be shown in that at the last attack the blood had reached pretty nearly the normal condition, and that was the end of the disease. This case will be reported in full.

DR. F. C. SHATTUCK: May I ask Dr. Stockton whether I understood him to say that these blood counts were made after each attack had run its course?

DR. STOCKTON: One count was during the paroxysm and two immediately after the paroxysms and at a time when we expected to find the leucocytosis at its height.

DR. A. H. SMITH: In regard to the statement just made by Dr. Stockton, is it not true that the leucocytosis is at its height just a few hours before the defervescence? Is there not a fall in the leucocytosis just before the decline of temperature, so that from this the decline of the temperature can with probability be predicted?

DR. STOCKTON: I do not understand that that is the case. I understand that, if you make an examination before the crisis or just at time of the crisis, you will find the leucocytosis at its height, but if examined some time afterward you will find a decline in the leucocytosis, though it will still be beyond the usual number.

DR. THAYER: In our experience there is considerable variation in the behavior of the leucocytosis in connection with the crisis in pneumonia. As Billings has shown, the fall appears to depend rather upon the resolution of the consolidation than upon the actual fall in temperature. While the fall in leucocytes may be very considerable and very rapid, and may occur coincidently with the crisis, in other instances, where resolution is slow, the leucocytes may fall to a normal point for days or even weeks. In most of our cases, however, there is a sudden fall, even though it may be relatively slight at the time of the crisis.

In some instances I have observed the disappearance or marked diminution of a leucocytosis even a little before the crisis. An increase in the number of leucocytes just before the crisis has not been the rule in our cases.

GASTRIC SYPHILIS, WITH THE REPORT OF A CASE OF PERFORATING SYPHILITIC ULCER OF THE STOMACH.

By SIMON FLEXNER, M.D.,
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CHIARI[1] opens his paper on "Gastric Syphilis," contributed to *Virchow's Festschrift*, in 1891, with the following remarks: "Although we are to-day sufficiently informed of the pathological changes caused by syphilis in most of the organs of the human body, and, thanks to the famous investigations of Virchow, we are able, in spite of our ignorance of the specific syphilitic virus, to identify the anatomical lesions of the disease, yet there are a few organs respecting which our knowledge of their syphilitic affections is not at all complete. To these latter organs belongs the stomach."

Chiari,[2] in his critical review of the reported cases of syphilis of the stomach up to the time of his publication, accepts as conclusive only those of Klebs, Cornil and Ranvier, Weichselbaum, and Birch-Hirschfeld. I shall follow Chiari in accepting these and rejecting the other reported instances, with the exception of Wagner's case, and I shall find in the meagre literature of the subject, especially in the English language, justification for the publication of the report of the present instance.

The case reported by Klebs[3] occurred in a man who showed, at the autopsy, besides an ulcer of the stomach, numerous ulcers and cicatrices of the skin, fresh ulcers of the pharynx, gummata of the lungs and liver, and ulcerating gummata of the intestine. He describes the gastric lesion somewhat as follows: The ulcer was situated on the

[1] "Ueber Magensyphilis." Festschrift, Rudolf Virchow, 1891, ii. 297. [2] Ibid.
[3] Handbuch der pathologischen Anatomie, 1869, i. 269.

posterior wall near the lesser curvature, two inches from the cardia. The mucous membrane was the seat of a circular erosion the size of a franc-piece, which resembled strongly similar ulcerations of the base of the tongue. The remaining tissues of the stomach were thickened in this place, the serosa especially showed a strongly circumscribed, smooth, tendon-like thickening, which, in the region of the base of the ulcer, presented a variegated yellow appearance. The diagnosis was confirmed by microscopical examination.

Cornil and Ranvier[1] report the case of a woman, aged thirty-nine years, in whom gummata were found in the liver and stomach. There existed in the stomach several flat tumors occupying the lesser curvature in the region of the pylorus. These were about 5 cm. in width and 12 mm. in depth, and the infiltration, having the character of gumma, involved the mucous membrane, submucosa, muscularis, and even the serosa, which was thickened.

The case of Weichselbaum[2] was in a man twenty-five years of age. The immediate cause of death was erysipelas. Syphilitic lesions existed in the cranium, nose, pharynx, larynx, liver, and stomach. The stomach exhibited a contracted cicatrix and two ulcers. The latter were on the posterior wall, above the greater curvature, and their bases were composed of cicatricial tissue. It is probable, but not certain, that the ulcers and cicatrix had originated in gummata.

Birch-Hirschfeld[3] has encountered four cases. They are as follows:

One was a woman, aged forty-five years. The syphilitic infection dated from six years before her death. For four years she had suffered from gastric symptoms. At the autopsy were found (1) a gumma of the liver the size of the fist; (2) in the anterior wall of the stomach, near the pylorus, an oval, yellow, firm plaque, 8 cm. long, showing slight ulceration. The base and edges consisted of firm cicatricial tissues, and the infiltration occupied mucosa and submucosa. The bloodvessels were obliterated.

The second case was a man who exhibited gummata of the lymph-glands, jejunum, and stomach. The last was of the nature of an ulcer situated at the cardia, the edges of which were dense and gummatous, the base clean.

[1] Manuel d'Histologie pathologique, 1884, ii. 296.
[2] "Syphilitische Geschwürs im Magen." Ber. d. Rudolfspitales in Wien, 1883, 883.
[3] Lehrbuch d. patholog. Anatomie, 1887, ii. 518, 537, 589.

The third instance was a male, thirty-five years old, infected four years previously, in whom were found gummata in the bronchial and mediastinal glands and small intestine, cicatrices in the liver, and an ulcer showing gummatous edges, affecting the lower end of the œsophagus and extending into the stomach. These three cases occurred in adults, presumably in all in consequence of acquired syphilis.

The fourth case of Birch-Hirschfeld was congenital in origin, and was a newly born child which presented lesions of skin syphilis and gummata in the liver and lungs. The pars pylorica ventriculi contained an elevated infiltration the size of the palm of the hand, white in color, and of firm consistence, consisting of a granulation tissue developed in the submucosa and mucosa. The granulation tissue was rich in epithelial cells and contained bloodvessels with thickened walls. Birch-Hirschfeld is of the opinion that the tumor was syphilitic in origin.

Chiari[1] paid especial attention to the occurrence of gastric syphilis, and in 243 cases which showed at autopsy anatomical lesions of syphilis he found 2 of undoubted gastric lues. The 243 cases included 145 of hereditary and 98 of acquired origin. One of the cases of gastric syphilis was of the inherited and the other of the acquired form.

The case of acquired syphilis occurred in a man twenty-three years of age. The clinical diagnosis was tuberculosis pulmonum, syphilis, and gastro-enteritis catarrhalis. The luetic infection dated from two years ante mortem. During the last year of life the patient had passed through an attack of syphilitic iritis and had had severe gastric symptoms. There was a large cicatrix on the glans penis. Gummata were present in the right lung, liver, kidneys, and intestines. The lung (right) and intestines showed lesions of tuberculosis. In both situations they were distinguishable from the syphilitic lesions. The stomach showed a chronic catarrhal condition in the region of the pars pylorica. In the region of the posterior wall, occupying the right side, and extending from the lesser to the greater curvature, there existed an almost circular loss of substance, 10 cm. in extent, that gave the impression of a peptic ulcer. The ulcer had perforated the

[1] Op. cit.

coats of the stomach in the central part, which was prevented from communicating with the peritoneal cavity by adhesions with the pancreas, the transverse mesocolon, and the lower part of the duodenum. Other infiltrated areas existed on the anterior wall near its middle. These projected above the surface, and upon microscopical examination they agreed with the syphilitic plaques in the intestine, with each other, and with the thickened edges of the ulcer. They are to be regarded as gummatous infiltrations, of which one had become ulcerated.

The instance of hereditary syphilis was in a boy three weeks old.[1] There were maculo-vesicular exanthem, pneumonia alba, gummatous cholangitis, and cholecystitis, gummatous plaques of the small intestine, osteochondritis syphilitica, and elevated plaques in the stomach. The general gastric mucous membrane was slightly injected; at several points it was thickened, pale-yellow in color, remarkably smooth, and protuberant. The thickening involved all the tissues, which, on section, presented a uniform, fibroid character. In some of the plaques central ulcerations existed. In all, five such growths were discovered. The microscopical examination showed a granulomatous tissue spreading from the submucosa into the other coats. A thick infiltration about the bloodvessels was noted. Necrosis was absent, but the structure of the gastric plaques agreed with the corresponding formations in the intestine and the nodules in the liver.

The next three reported cases are of the inherited form, and also emanate from Chiari's laboratory. Bittner[2] describes these cases, which arose within a period of one year. The first was a male child, which lived two and one-half hours. The anatomical diagnosis is given as pneumonia alba, chronic splenic tumor, osteochonditis syphilitica, and gummata of the liver, intestine, and stomach. In the last organ there were several discrete plaques occupying the anterior wall. These structures consisted of a granulomatous tissue, in which large, round and spindle-cells were found, which originated in the submucosa and extended into the mucous membrane. The

[1] "Lues hereditaria mit gummöser Erkrankung des gallsleitenden Apparates und des Magens." Prager medic. Wochenschrift, 1885, No. 47.

[2] "Zur Kenntniss der gummösen Magensyphilis." Prager medic. Wochenschrift, 1893, xviii. 581.

second was a fœtus of the sixth month. In it were found pemphigus, gummata in both lungs and in the liver, osteochondritis syphilitica, plaques in the small intestine, and a superficially ulcerated, infiltrated focus, the size of a pea, in the stomach, which had all the characteristics of gumma. The third case was a stillborn fœtus. The liver and adrenals contained gummata and the stomach thickened areas, which upon microscopical examination presented the appearance of syphilitic granulation tissue, developed especially in the submucosa and mucous membrane.

From 1893 to 1896 there appears to be a complete break in the literature of this subject. In this year appeared Stolper's[1] monograph on *Visceral Syphilis*, in which he describes a case of gastric syphilis. This case came to autopsy in the pathological institute in Breslau, and was the only instance of syphilitic affection of this organ in 86 cases (25 inherited, 61 acquired) of anatomical syphilis which had been examined post mortem in the institute during three years (1892-1895). It was an example of acquired lues.

The case was a man, forty-three years old. The anatomical diagnosis was: inveterate syphilis; cicatrices on penis; chronic fibroid pneumonia, purulent bronchitis, and bronchiectasis; cicatricial stenosis of trachea and larynx; atrophy at base of tongue; chronic and acute lymphadenitis; lobulated liver; ulcerated gummata of stomach.

The stomach was not dilated, and the general mucous membrane was free from thickening. The posterior wall of the organ showed an elevated area of elongated form, consisting of two converging bands which ran in its long axis. These could be covered by two fingers, and in the more elevated places they were the seat of pigmentation and multiple small ulcerations. These "convolutions" gradually became incorporated with the mucosa of normal thickness. The superior one measured 5 cm., the inferior about 10 cm. in length. The peritoneal coat was not thickened over the bands. On section the submucosa appeared greatly thickened, the mucosa in the region of the ulcers was destroyed, and elsewhere was invaded by the submucous infiltration. The microscopic examination showed the pathological process to be located chiefly in the submucosa, and the necrosis and ulceration of the mucous membrane to be the result of the oblit-

[1] "Beiträge zur Syphilis Visceralis (Magen-, Lungen-Herzsyphilis)." Bibliotheca Medica, 1896, C. Heft 6.

eration of bloodvessels passing to it. The new tissue differed from that described by other writers in that it was dense, contained few stainable cells and nuclei, presented in some places a fibrillated myxomatous and in others a definite necrotic appearance. The diagnosis is regarded as certain, because of the other typical syphilitic lesions in the body, and also because of the peculiar structure of the gastric lesion.

The doubtful example of Wagner[1] was of the acquired form, and was found in a man fifty-eight years old, in whom there was also noted syphilitic papilloma of the larynx. The gastric lesions consisted of three elevated and infiltrated foci, the largest being situated on the posterior wall of the stomach a short distance from the pylorus. The lesions were regarded by Wagner as syphilitic, although the microscopical appearances are not given by him.

This review contains the authentic cases of syphilitic lesions of the stomach which I have been able to find in the literature. It covers fourteen cases, of which number five were of the inherited and nine of the acquired form. From it will be seen that no instance of the disease has been recorded by writers in the English language; indeed, the proceedings of the London Pathological Society do not contain a single reference to such a disease. Further, with one exception—that of Cornil and Ranvier—the entire literature is German.

The case which I have to report is that of a male, fifty-two years of age, whose illness extended over a period of three years. The man was a patient of Dr. Irving Miller, of Baltimore, to whom I am indebted for the main clinical history and for the privilege to do the autopsy. He was in the hospital on two occasions, but only remained to be examined; he was not treated there.

Dr. Miller writes: "I first saw the patient in August, 1892. At that time he was a large, fairly well-nourished man, about six feet in height and weighing 170 pounds. His average weight was 200 pounds. His occupation was that of a showman. The first appearance of his illness was at the preceding Christmas, while filling an engagement in Boston, and followed a drinking-bout and exposure. It was ushered in by a severe spell of vomiting, which persisted for several days, and was followed by irregular chills. This condition of affairs continued off and on until the summer, when I first saw him. At this time the temperature ranged around 101° F.; there was a tumor in the splenic region, extending 9 cm. below the costal margin and forward nearly to the umbilicus. Exquisite tenderness was present all over the area of dulness. I regarded the tumor as being the enlarged spleen. The urine

[1] "Das Syphilom." Arch. d. Heilkunde, 1863, iv. 225.

contained bile-pigment, and there was some pigmentation of the skin Neither sugar nor albumin was found in the urine. There was little change in the conditions noted for several months, when the splenic tumor was found to have diminished markedly and ascites to have appeared. The dropsy increased, involving the legs and scrotum. The patient was tapped for the first time on April 20, 1893; three and one-half gallons of fluid were withdrawn. The tapping was repeated at intervals of six days to two weeks, the amount of fluid withdrawn varying from two to six gallons. The relief afforded by the paracentesis was so great that the operation was resorted to to enable the patient to go fishing the next day. The accumulation of fluid continued for two years, and then began to diminish, until very little fluid could be detected in the abdomen. Purges were occasionally administered. The morphine habit was acquired. The night before his death the patient dined abundantly on fried crabs and ice cream. When I saw him, a few hours before his death, there were intense abdominal pain and tympanites. Pulse thready, weak, 130 to the minute; profuse sweating. He died in the early morning."

The patient had been in the hospital on two occasions—in February, 1893, and March, 1894—for examination. On his first entrance Dr. Hewetson found a full abdomen, no increase of liver dulness, the spleen enlarged and palpable three-fourths of a hand's breadth below the costal margin. When he returned in 1894 he reported having been tapped at intervals of about ten days, in all sixty-five times. After the removal of 9700 c.cm. of fluid the liver could be felt below the ensiform cartilage; it was hard and apparently bound down by adhesions. A probable diagnosis of hepatic cirrhosis was made.

The autopsy was performed eight hours after death on a warm day in June. The anatomical diagnosis was: Old adhesions between liver, stomach, spleen, and pancreas. Large hepatic gumma. Syphilitic ulcer of the stomach with perforation. Acute diffuse, sero-fibrinous, and gaseous peritonitis.

Only such parts of the protocol as bear on the subject of the paper are given. The peritonitis, it may be remarked, was caused by a mixture of the bacillus aërogenes capsulatus, the bacillus coli communis, and the streptococcus, the first organism predominating.

The omentum was greatly shortened, the small intestine contracted, and the general serous surfaces were thickened. The loops of the jejunum and ileum were particularly firm and rigid. The spleen was much enlarged, measuring 12 x 17 x 6 cm.; capsule opaque and cartilaginous. No gummata. It was bound firmly to the fundus of the stomach and covered by the very closely adherent omentum. The latter structure contained little fat, appeared as a mass of tatters, and was gathered together at the left border of the stomach, with which organ and the spleen it was firmly united. In gently separating the adhesions in this region the stomach contents were seen to issue from a small opening in this organ. They agreed with the material found in the peritoneal cavity when it was first opened. The wall of the stomach in this situation was firm and board-like, and on being dissected

away from the spleen was found thickened out of all proportion to the rest of the organ. The perforation had taken place below the splenic adhesion and at a point uncovered by complete omentum.

On opening the much contracted stomach the general mucous membrane presented a mammillated appearance; but in the fundus, 4 cm. from the œsophageal opening and occupying the greater curvature, a large ulcer, measuring 5 x 5 cm., was found. The base of this over most of the central part was the muscularis; the edges were thick, polypoid, and firm, and the perforation was 15 x 3 mm. in size. Just about the perforation the tissues presented a greenish and necrotic appearance (Plate I.).

The liver was bound to the diaphragm; its capsule was thick and cartilaginous. The left lobe was reduced to a mere appendage, but it was firm and nodular. The right lobe was not especially reduced in size. On section of the organ the remnant of the left lobe was occupied by a mass formed by the confluence of several gummatous nodules, and the mass extended well into the right lobe along its lower border. The tumor thus formed lay over the portal vein, which was thick and white in color as it entered the porta of the liver, and passed upward to the summit of the liver between the lobes and impinged on the vena cava. The dimensions of the tumor were 11 x 4 x 5 cm. The gummata were of perfectly characteristic appearance, and, on histological examination, presented the usual structure. Gummata were not found in other organs.

For the purpose of the microscopic study pieces of the ulcer from several different parts were subjected to examination. The principal microscopic characters are as follows: The pathological process is localized chiefly in the submucosa and exists in two distinct stages. The earlier stage is less frequently met with, and consists of a cellular infiltration of the submucosa, through which the tunic is rendered much thicker than normal. The cells belong, in general, to the type of granulation-tissue cells, many of which are large and epithelioid in appearance. They are interpolated between the old connective-tissue fibrils and collected into large, more independent foci. The infiltration extends from the submucosa into the muscular coat, and to a much less degree into the mucous layer. The muscularis mucosa is for the most part the limiting line above. Within the large cellular accumulations foci of necrosis occur. These are quite large and consist of centres of coagulation necrosis, in which much fragmentation of nuclei and emigrated polymorphonuclear leucocytes are prominent features. The form of necrosis is consistent either with tuberculosis or syphilis; in its acuteness it resembles that seen in the former disease. The necrotic foci extended freely into the muscle and not at all into the mucosa. The bloodvessels in this situation show a simple infiltration of the adventitial coat, except in the necrotic areas, where they are obliterated.

The later stage is more common, and is what is met with in all parts of the ulcer and the tissue forming its elevated boundaries. It consists of dense fibrous tissue, which again is developed chiefly in the submucosa, and

then extends into the muscular tunic. Scattered granulation-tissue cells are found among the developed fibrils. The bloodvessels are extensively diseased; endarteritis and endophlebitis obliterans, and hyaline thrombosis with organization are common. The serous coat, too, is thickened, and in some places about the adhesions greatly so.

The base of the ulcer is covered to some extent with mucous membrane, and only in its centre is it bare. The muscular coat is exposed in this part, and the more superficial fibres are quite necrotic. The elevated edges of the ulcer are clearly not the remains simply of the old mucosa and submucosa. This is proven by comparison with the surrounding intact mucosa, which is much less elevated. The microscopic examination shows the thickening to be due to a new development of dense fibrous tissue, such as was described in the later stages of the general pathological process.

There can, I think, be no doubt that the ulcer is of syphilitic origin: the character of the new tissue and the form of cell-death met with seem sufficient proof for this belief. But I think it much more improbable that it is due to the softening of a gumma. Indeed, I find very little evidence in support of such a view. On the other hand, the appearances described speak more for an indirect form of necrosis of the mucous membrane, brought about by the combined softening of submucous gummatous infiltration and the obstruction and obliteration of bloodvessels in the same situation. The mucous membrane thus deprived of its nutrition became necrotic, was removed, and the ulcer resulted. The submucosa suffered either directly through necrosis of the infiltrating cells, or, again, indirectly, owing to the vascular changes combined with the action of bacteria.

The clinical course of the disease is made clear by the autopsy findings. The splenic tumor and ascites were the results of the portal obstruction; the obstructing agent was the syphilitic tumor. It seems reasonable to suppose that the gumma was larger at one time than it was at the autopsy, and that the reduction of the ascites was owing to this change. The evidence for this might be found in the size of the left lobe of the liver, and is strengthened by the absence of a marked collateral circulation. The immediate cause of death was the perforation into the peritoneal cavity of the gastric ulcer in a part unprotected by adhesion with surrounding structures.

EXPLANATION OF PLATE.

The stomach is laid open along the lesser curvature. The drawing, which was kindly made by Dr. Livingood, is of natural size.

Gastric syphilis. Stomach laid open along the lesser curvature.

A RÉSUMÉ OF EXPERIMENTAL STUDIES ON THE PREPARATION AND EFFECTS OF ANTITOXIC SERUM IN TUBERCULOSIS.

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The brilliant and beneficent results which have followed the discovery and use of the diphtheria and tetanus antitoxic serum have stimulated similar research in many of the infectious diseases. But the work in other fields has led to results which, in their practical phases at least, are as yet disappointing.

Among the infectious diseases to which attention was early turned in the studies on artificial immunity, tuberculosis is one which presents aspects at once attractive and forbidding. Although workers in the field have not been idle, it must be conceded that the attempts to provide a curative or antitoxic serum for tuberculosis have not thus far been such as to inspire the confidence of those fitted by technical training and clinical experience to judge.

Simultaneously with the development of tetanus and diphtheria antitoxin, even earlier (1888), Hericourt and Richet[1] reported favorable results in conferring immunity to tuberculosis in rabbits by injections of the serum of immunized dogs. Unfortunately, clinical tests of the efficacy of this serum when applied to human tuberculosis did not prove at all encouraging. Nevertheless, the efforts of experimenters to advance existing knowledge of the toxic products of the tubercle bacilli, to produce an artificial immunity against tuberculosis in animals, and to obtain an antitoxic serum for this disease, have been steadily carried on, and some light has been thrown on this all-important and complex problem.

One of us (Trudeau)[2], [3] has been engaged in attempts at producing

mmunity to tuberculosis since 1891; the present paper, however, includes only our studies with serums, which were commenced in 1894. While confessing our disappointment at the outcome of most of these experiments, we yet feel warranted in presenting them, because they seem to us to indicate some interesting phases of work in tuberculosis and the care needed to make safe deductions from laboratory experiments.

The efficacy of any antitoxin serum and the ease with which it is obtainable would seem, judging by analogy, to be in direct ratio to the degree of toxicity possessed by the poison against which protection is sought. For this reason, to produce and demonstrate antitoxic properties in serums would, *à priori*, seem to be more difficult in a disease so chronic as tuberculosis on account of the low dergee of toxicity of its products. The antituberculous serums which we have produced by our own methods, the antitoxic power of which could be proved experimentally on animals, and our tests of the antitoxic properties in the serums produced by others, have shown only slight potency for any of them up to the present time. Tuberculosis does not belong to that class of infectious diseases which kill by acute toxæmia, but to the class to which syphilis, actinomycosis, and leprosy also belong, and which destroy life, not only by the chronic and long-continued systemic poisoning they produce, but by the pathogenic changes brought about through the localization and growth of the germs in organs necessary to life.

Koch's[4] assumption seems plausible, that immunity to the toxic products of the tubercle bacillus does not necessarily imply immunity to tuberculosis, and a serum which would neutralize the toxic effects of tuberculin may not prevent the growth of the tubercle bacillus in the tissues and its destructive action on the organs of the body. An efficacious serum for this disease would probably require, therefore, to possess not alone antitoxic but also germicidal properties, or at least the power to excite the organism to germicidal activity. Bactericidal properties have been claimed for certain serums by careful observers, but the specificity of any such action is open to question; and the existence of any demonstrable degree of germicidal power in antituberculous serums has not been confirmed generally by other observers.

It is not at all certain that, even if bacterial immunity could be produced by any method, the serum of animals possessing this immu-

nity would necessarily be either antitoxic or germicidal. Indeed, one of us (Trudeau) has succeeded in producing a marked degree of immunity in rabbits by preventive inoculation of living cultures of tubercle bacillus attenuated by prolonged cultivation; and yet the serum of these animals which had resisted a subsequent virulent inoculation proved to have but slight, if any, antitoxic power, and did not seem to influence to an appreciable degree the course of the disease in tuberculous guinea-pigs.

Notwithstanding the meagre results obtained in animal experiments, a good deal of clinical evidence as to the value of serum treatment in tuberculosis has been presented, which, however, is not sufficiently encouraging to be convincing; since this disease runs, without any specific treatment, so varied and erratic a course. The clinical evidence has not been considered in this research, and must be judged by itself. These studies have been entirely confined to such experimental proof of the presence of curative and antitoxic properties in serums as could be obtained by laboratory methods.

The nature of the bacterial poisons used in injecting animals with a view to producing curative serums is probably of vital importance to the success of such attempts.

When we began this work the observations of Hammerschlag,[5] Koch,[6] Proskauer and Brieger,[7] Hueppe and Scholl,[8] Weyl,[9] Hericourt and Richet,[10] Crookshank and Herroun,[11] Richet,[12] Bâbes,[13] Zuelzer,[14] Klebs,[15] Hahn,[16] Kühne,[17] Hoffman,[18] Matthes,[19] de Schweinitz,[20] and our own, agreed in the main as to the presence of poisonous albuminous substances in cultures of tubercle bacillus which were products of the germ-growth and had chemical reactions like the albumoses, albuminates, and nucleo-proteids,* and all producing the characteristic physiological action of tuberculin. It is to be noted that large quantities of the filtered culture-fluid are borne by healthy animals without immediate toxic effects, while quite small doses may produce death in tuberculous animals within a few hours.

No material addition to our knowledge of these culture-products has been published to the present time. Behring[21] has recently reported the separation of a more active poison than hitherto obtained.

* A single phosphorus determination, kindly made for us by Prof. R. H. Crittenden, of the pure proteid obtained from cultures on synthetic media (containing no peptone nor albuminoid) gave a content of 1.52 per cent. This indicated the presence of considerable nucleo-proteid produced by the tubercle bacillus.

De Schweinitz and Dorset[22] have prepared small quantities of a necrotizing substance. More recently Hahn[23] obtained from crushed living tubercle bacilli a juice having the properties of a hydrolytic ferment. The tubercle bacillus has been found by de Schweinitz,[24] Koch and Proskauer,[4] and Unna[25] to contain considerable quantities of fat and cellulose, the former having the specific staining reaction. The whole subject evidently requires exhaustive study.

The experiments with dead tubercle bacilli and their extracts by Wyssokowicz,[26] Maffucci,[27] [28] Daremberg,[29] Prudden and Hodenpyl,[30] Koch,[6] Straus and Gamaleia,[31] Vissman,[32] Kostenitch,[33] Grancher and Martin,[34] Grancher and Ledoux-Lebard,[35] Freudenreich,[36] Masur and Kockel,[37] Abel,[38] Carriére,[39] Sciolla,[40] and Bâbes and Proca,[41] show their marked capacity to stimulate local cell-growths, to produce tubercles, local necrosis, aseptic abscesses, cachexia, with grave disturbance of the blood-forming functions, and nephritis. In the face of these facts it seemed hardly probable that the use of cultures containing tubercle bacillus, living or dead, would be practicable to create an increased tolerance. At least it appeared unlikely that animals would tolerate doses presumed to be necessary in order to originate antagonistic substances. That the tubercle bacillus substance is necessary to produce immunity was later claimed by Koch[4] in experiments with tuberculin "R."

We have endeavored to cover many but not all aspects of this subject in our experiments, and our methods have varied in some respects from those of other workers in this field whose developments we have followed. Without further discussing the theoretical considerations concerned, we will proceed to the description of our work.

The studies included in Part I. relate to the methods adopted by us in attempts at producing the sought-for immunity in various animals, and the tests of the germicidal and curative properties which might be possessed by the serum of animals thus immunized. The studies included in Part II. relate to tests in animals of the antitoxic power of serums in tuberculin poisoning.

Thus far we have employed sheep, fowls, asses, and rabbits in attempts to obtain antitoxic serum. Before giving details of the work the following summary will set forth the general methods employed by us to obtain the serums.

PART I.

1. Sheep repeatedly inoculated intravenously with filtrate of tubercle bacillus cultures on thymus bouillon.

2. Fowls repeatedly inoculated intraperitoneally with tubercle bacillus of mammalian tuberculosis of increasing virulence, and recovered.

3. Sheep injected subcutaneously with increasing doses of tuberculin.*

4. Sheep repeatedly inoculated intravenously with living non-virulent cultures of tubercle bacillus.†

5. Ass repeatedly inoculated intravenously with living non-virulent cultures of tubercle bacillus.

6. Ass inoculated: (*a*) Subcutaneously with virulent living cultures of tubercle bacillus; (*b*) intravenously with virulent tuberculous material, and recovered; (*c*) treated with tuberculin subcutaneously in increasing doses.

7. Ass injected: (*a*) Subcutaneously with dead cultures of non-virulent tubercle bacilli on thymus bouillon; (*b*) with precipitated tuberculin from proteid-free culture media of same non-virulent tubercle bacillus; (*c*) alkaline extracts of the bacilli with dead bacilli subcutaneously; (*d*) living non-virulent tubercle bacilli.

8. Rabbits: (*a*) Inoculated intravenously with non-virulent tubercle bacillus and recovered; (*b*) inoculated intraperitoneally with virulent tubercle bacilli and recovered.

With serums from the foregoing we tried to carry out the following series of tests:

1. Effect of serum on healthy animals.

2. Treatment of tuberculous animals with serums to show influence on course of disease and temperature.

3. Test of germicidal influence *in vivo* and *vitro*.

* The tuberculin used in this work was made from full-grown bouillon cultures of non-virulent tubercle bacillus, evaporated over water-bath to one-tenth volume and filtered through clay; 0.100 c.c. usually sufficed to kill guinea-pigs six weeks tuberculous.

† The cultures denoted "non-virulent" were from tubercle bacilli grown four years in the incubator, and only occasionally killed guinea-pigs in six months to one year.

PART II.

Tests of antitoxic power of serums in tuberculin poisoning.

In these experiments we have considered:

1. Fatal doses of tuberculin* in sound animals.
2. Fatal doses in tuberculous animals.
3. Small doses in tuberculous animals to show effect: (*a*) On temperature; (*b*) local reaction.

We must acknowledge at the outset that for various reasons we were unable to carry out all of these tests with all of our serums, and the work is incomplete to that degree. Methods used in some tests were changed in others, because thought to be fallacious; particularly in testing for anti-tuberculin. Consequently there is no true basis for comparison for all the serums tried. In addition to the serums prepared by ourselves, we have tried five or six from other sources. In the present uncertain state of serum-therapy for tuberculosis it is undesirable to mention the names of their originators.

Many difficulties present themselves in any attempt to demonstrate a specific antitoxin in tuberculosis by methods analogous to those used so satisfactorily in diphtheria. The principal of these relate to the difficulty of obtaining a highly poisonous product in small bulk unless tuberculous instead of sound animals are employed for the tests.

Objections can easily be made to the use of tuberculin and diseased animals for testing serums. In the first place, tuberculin when prepared by boiling heat may not represent the unaltered toxins of tuberculosis, though containing more toxic extractive substances from the bacilli than when made by evaporation of cultures at low temperatures. Yet we cannot safely say that tuberculin is a wholly altered product until we have further knowledge of its chemical nature. We know, indeed, that boiling heat, not too prolonged, does not destroy its most prominent physiological action on tuberculous animals. The propriety of using tuberculin in serum tests principally depends upon the view one may take of the character of the peculiar reaction. That question may need further elucidation, but it seems to us that the best explanation we have from observations up to date supposes tuberculin to be a *partly specific irritant both to tuberculous foci and to*

* Under the term "tuberculin" we here include the various extracts of tubercle bacillus, but usually the original Koch fluid.

the susceptible organism in general. The local and general reaction is partly caused by the poisons contained in the tuberculin which irritates the sensitized cells composing the tubercle, and partly by those toxins set free by the hyperæmia or the enzyme action directly or indirectly produced by the dose of tuberculin (see Bâbes and Proca).[41] Whether the toxins liberated are the same, chemically, as those obtained from artificial cultures of tubercle bacillus, it is not easy to determine; but that some are set free seems obvious from the profound general disturbance brought about by a minute dose of tuberculin. According to this theory, the poisons are stored up in the tubercles, and in part, at least, derived from the dead or weakened bacilli, as shown by Bâbes and Proca[41] in experiments with dead tubercle bacilli. Crookshank and Herroun[11] and Matthes[19] have extracted albuminous poisons out of caseous material from tuberculous lesions which had the properties of tuberculin. Kahler[44] and Lenoir[45] found albumoses in urine of patients being treated with tuberculin, which produced tuberculin reactions and were present in the urine in excess of that injected as tuberculin. Thus we have some evidence of the discharge of accumulated pyrogenic substances, and that the tuberculin injected in the minute dose necessary to cause the reaction may not itself play the prominent part as a poison, but rather as the excitant to the discharge of other specific poison.

Therefore, but for the uncontrollable amounts of hoarded toxin, as it were, exploded, coupled with the local congestions, there would be no objection to proving the activity of serums in this way. Given the serum of a tuberculous animal having been treated with tuberculin, and tolerating the reactions well, we might hope, if an antitoxin had been in the serum, that it would be effective against the specific poisons developed in the animal body by tuberculosis, though not necessarily against tuberculin as obtained from cultures. By analogy, such an antitoxin ought also to manifest its activity on other tuberculous animals injected with a dose of tuberculin just large enough to barely produce a reaction (and, at the same time, with a dose of such serum sufficient to surely neutralize it). Should it be weak in activity it would still seem possible to obtain some effect in that way. Furthermore, it might reasonably be expected that the fatal effects of doses of tuberculin just sufficient to cause death in tuberculous animals with uniform lesions might be inhibited by the administration of an efficient

serum, or, at least, that the lives of the animals might be appreciably prolonged. Such tests ought to give qualitative results, though, from the unknown quantities of toxin to be dealt with, manifestly they would not serve as quantitative standards for serums.

On the other hand, healthy animals cannot be suitable for tests until we can obtain sufficiently toxic unaltered products of tubercle bacilli; while if the serums proved to be wholly or chiefly bactericidal and not antitoxic, they would not reveal that fact in non-tuberculous animals.

As is well known from Koch's original experiments, healthy guinea-pigs tolerate very large doses of tuberculin. This fact renders it necessary to employ such a quantity of ordinary tuberculin to produce death that the effects of the unaltered ingredients of the culture fluid, such as glycerin, albumoses, or peptone, should be remembered, as well as the shock produced by the traumatism of voluminous injections.

We occupied ourselves for some time in attempts to produce a concentrated tuberculin or toxin from cultures; but while it is comparatively easy to produce tuberculin, even from non-virulent cultures, which will usually be fatal in doses of 1 c.c. to 100 grammes of pig, the strength of toxin mentioned by Maragliano[46] as used to test his serum, yet this ratio did not suffice to kill pigs weighing above 250 grammes in our experiments. In addition to the objections mentioned, we found its absorption from under the skin very uncertain.

We then sought, by precipitation from cultures on proteid-free media, to obtain a pure toxin which would be fatal in small doses. We also attempted to procure a concentrated poison from the bacilli by using weak alkaline extracts, but none of our preparations were quickly fatal to healthy animals in small doses, though producing cachexia and death after some time. After testing various preparations subcutaneously and intraperitoneally without encouragement, we abandoned the idea of utilizing healthy animals for antitoxin or antituberculin tests. In the course of this work we had used fifty guinea-pigs, weighing from 150 to 450 grammes. More recently fresh extracts from crushed living tubercle bacilli gave no more uniform fatalities.

Clinical experience with human tuberculosis confirms the fact that the poisons are of relatively low toxicity—where their immediate effects are considered—as compared with those of diphtheria, tetanus,

etc. The same fact suggests itself as a reason for the indifferent results of experiments in serotherapy with tuberculosis. The effect of tuberculin administered to an animal after the disease becomes established is, nevertheless, so powerful and the dose so small that the objections mentioned do not enter.

A surely fatal dose of tuberculin for a tuberculous guinea-pig, though not uniform, is small enough for testing serums; yet there are other factors not to be disregarded in such experiments which are very difficult to control. The local reaction varies considerably in intensity in the same series of animals. Differences in virulence of the inoculation-material used, variations in lesions, extent of caseation, age, and pregnant state of animals, suffice to require large numbers of experimental animals in any work on tuberculosis. All these factors we found especially important in testing for antituberculin.

For the reasons mentioned, the fatal doses of tuberculin necessarily vary. Differences in stage of disease, the injection of serums mixed with tuberculin or given separately may produce diverse results, owing to different rate of absorption* or other reasons. We also found that non-tuberculous serums and even physiological salt solution, when used under like conditions, gave results that dampen over-enthusiasm in making deductions. Yet in the experiments that follow, in the course of which two hundred and fifty pigs were used, there can be seen indications of a favorable influence or possibly antitoxic effect from some of the serums on tuberculous guinea-pigs tested with fatal doses of tuberculin.

Details of Methods Used to Test Antitoxic Power of Serums.

The guinea-pigs were inoculated in lots of ten to twenty, at different times, with cultures or other tuberculous material of varying known virulence. The point of inoculation was usually below the right groin in the subcutaneous tissue.

The tuberculin used to kill varied in dose from 0.100 to 0.500 c.c., according to stage and type of disease in the animals, and was made

* The slow absorption of the infiltration produced by injections under the skin of guinea-pigs, of sheep, cow, ass, and rabbit serums, was a point specially noted by us in all this work, and has been of late particularly contrasted with the better absorption of horse serum by Uhlenhuth.[42]

from non-virulent bouillon cultures. The same bottle was used in nearly all the tests. For effect on temperatures, doses of 0.001 to 0.002 were employed.

The doses of serum ranged from 1 to 12 c.c. Some lots were tested with doses of serum and tuberculin proportioned to the weight of the pigs.

Loss of weight and strength were taken as the most practical criterions of condition of the diseased animals at the time of testing.

The tests were made from twenty-one to fifty-six days after infection.

To avoid false deductions from lack of absorption of tuberculin when mixed with serum, it was given separately in most of the experiments.

Serums were injected at the same time or before the tuberculin, subcutaneously, and in some instances intraperitoneally; the tuberculin always under the skin. Temperatures were taken in the rectum at the time of injection and six hours later. Some surviving animals were usually killed for comparison after twenty-four hours.

Normal horse serum, diphtheria antitoxin, normal sheep serum, 0.6 per cent. NaCl solution and hydrocele fluid were used to control antituberculosis serums in comparative tests.

Résumé.

The results of our four-years' work in experiments upon four sheep, three asses, twelve fowls, eighteen rabbits, and four hundred and fifty guinea-pigs, are to be found in the following summary:

1. Sheep injected intravenously with killed thymus cultures: Result so unsatisfactory that the serum-tests were not conclusive of its value.

2. Chickens inoculated intraperitoneally with mammalian tuberculosis: Serum revealed no germicidal or inhibitive action on tubercle bacillus, nor favorable influence on the course of the disease in guinea-pigs.

3. Sheep injected with tuberculin: The serum was wanting in germicidal, antitoxic, or curative effect, so far as tested.

4. Sheep inoculated intravenously with non-virulent cultures: Cachexia followed, and, therefore, the serum was not used.

5. Ass inoculated as in 4; died from pulmonary embolus: Serum not bactericidal to tubercle bacillus.

6. Ass inoculated with virulent tubercle bacilli, treated with tuberculin and recovered: The serum showed no germicidal nor curative but possibly some antitoxic effect.

7. Ass inoculated with non-virulent tubercle bacilli and treated with various extracts of tubercle bacilli and dead bacilli: Serum showed no activity.

8. Rabbits inoculated with non-virulent and virulent tubercle bacilli and recovered: Serum possibly conferred some protection in tuberculin poisoning, and possibly prolonged lives of treated guinea-pigs.

Although we have a full appreciation of the uncertainty of correct conclusions from tests of the serums other than our own product, which were tried with tuberculin, only one indicated slight antitoxic power. This was obtained from a horse inoculated with non-virulent cultures.

That the apparent protection against fatal tuberculin poisoning occasionally seen was not necessarily from specific antitoxic power of the serum is made probable by the similar effects of physiological salt solution shown at times.

None of the serums appeared to prevent the local or general reaction from small doses of tuberculin, nor influence the temperature of tuberculous animals.

Disappointing as these results may seem, the writers feel that, in the light of recent contributions made by Ehrlich, Wasserman, and Behring[43] to our knowledge of the mechanism of immunity and antitoxin production in the body, the outlook for an efficient tuberculosis antitoxin is by no means a hopeless one.

In conclusion, we would express our thanks to Drs. S. W. Hewetson, W. S. Nelson, and J. A Wilder, all of whom have aided in the many arduous details of these experiments.

April 1, 1898. The full details of this work, more especially the experimental work which forms the basis of this paper, will be published in the *American Journal of the Medical Sciences.*

REFERENCES.

1. Héricourt et Richet. De l'immunité conférée à des lapins, etc. Etudes exper. et clin., etc. Verneuil, 1888-90.

2. Trudeau, E. L. An Experimental Study in Preventive Inoculation in Tuberculosis. Medical Record, November 22, 1890.

3. Trudeau, E. L. Eye Tuberculosis and Antitubercular Inoculation in the Rabbit. New York Medical Journal, July 4, 1893.

4. Koch, R. Ueber neue Tuberculin prepärata. Deutsch. med. Wochen., No. 14, 1897.

5. Hammerschlag. Bacteriologisch-chemische Untersuchungen über Tuberkelbacillen. Central. f. klin. Med., 1892, p. 9.

6. Koch, R. Weitere Mittheilung über das Tuberkulin. Deutsch. med. Wochen., No. 43, 1891.

7. Proskauer u. Brieger. (Ref. by Koch. Analysis of Tuberculin.) Deutsch. med. Wochen., No. 43. 1891.

8. Hueppe, F., u. Scholl, H. Ueber die Natur der Koch'schen Lymph. Berlin. klin. Wochen., Nos. 4–8, 1891.

9. Weyl, Th. Zur Chemie und Toxikologie des Tuberkelbacillus. Deutsch. med. Wochen., No. 7, 1891.

10. Héricourt et Richet. De la toxicité des substances solubles des cultures tuberculeuses. Compt.-Rend. Hebd. Soc. de Biol., No. 21, 1891.

11. Crookshank, E. M., and Herroun, E. F. On the Chemical Properties and Physiological Effects of the Products of the Tubercle Bacillus in Pure Cultivation. British Medical Journal, February 21, 1891.

12. Richet. Ch. De la toxicité des substances solubles des cultures tuberculeuses. La Semaine Méd., No. 31, 1894.

13. Bâbes, A. et V. Sur certaines substances chimiques produites par le bacille de la tuberculose et sur tuberculose aviaire. Congrès p. Tuberculose, 1891.

14. Zuelzer. Ueber ein Alkaloid der Tuberkelbacillen. Berlin. klin. Wochen., No. 4, 1891.

15. Klebs E. Die Causale Behandlung der Tuberkulose. Hamburg, 1894.

16. Hahn, Martin. Ueber die Chemische Natur des wirksamen Stoffes in Koch'schen Tuberculin. Berlin. klin. Wochen., No. 30, 1891.

17. Kühne, W. Erfahrungen über Albumosen und Peptone. Zeitsch. f. Biologie, Bd. xi. 1, xii. 2.

18. Hoffman, R. R. Zur Kenntniss der Eiweisskörper in dem Tuberkelbacillen. Wiener klin. Wochen., No. 38, 1894.

19. Matthes, M. Ueber die Wirkung einiger subcutaneinverleibter Albumosen, etc. Deutsch. Archiv f. klin. Med., 1894.

20. de Schweinitz, E. A., and Dorset, M., et al. Tuberculosis Investigations. Bull. U. S. Bureau of Animal Industry, Nos. 7 and 13.

21. Behring, E. Ueber experimentelle begründete aetiologische Therapie. XV. Cong. f. innere Med., Berlin, 1897.

22. de Schweinitz, E. A. Some Products of the Tuberculosis Bacillus and the Treatment of Experimental Tuberculosis with Antitoxic Serum. Transactions of the Association of American Physicians, 1897.

23. Hahn, Martin. Immunisirungs und Heilversuche mit den plasmatischen Zellsäften von Bacterien. München. med. Wochen., No. 48, 1897.

24. de Schweinitz, E. A., and Dorset, M. The Composition of the Tuberculosis and Glanders Bacilli. Journal Amer. Chem. Soc., August, 1895; March, 1896.

25. Unna. Feltgehalt de Tuberkel und Leprabacillen. (Abstr.) München. med. Wochen., No. 5, 1897.

26. Wyssokowicz. (Injections of Dead Bacilli. Ref. Masur et Kockel.) Separat-ab. aus Mittheil. aus Dr. Brehmer's Heilanstalt, etc. Wiesbaden, 1890.

27. Maffucci, A. Ueber die Wirkung der reinen, sterilen Culturen des Tuberkelbacillus. Central. f. allg. Path. u. path. Anat., No. 26, 1890.

28. Maffucci, A. Ueber die Wirkung der Produkte des Tuberkelbacillus. Deutsch. med. Zeitung, No. 24, 1892.

29. Daremberg, G. Reaction des subjets tuberculeux sous l'influence des liquides de l'organism sain. Compt.-Rend. Hebd. Soc. de Biol., vol. v., December 30, 1893.

30. Prudden, T. M., and Hodenpyl, E. Studies on the Action of Dead Bacteria in the Living Body. New York Medical Journal, June 6 and 20, 1891.

31. Straus, J., et Gamaléia, N. Recherches expérimentales sur la tuberculose, etc. Arch. méd. Exp. d'Anat. Path., vol. iii., No. 4, 1891; Etudes, etc., sur la Tuberculose, vol. iii. p. 433.

32. Vissman, W. Wirkung todter Tuberkelbacillen und des Tuberkulins auf den Thierschen Organismus. (Thesis, Berlin, 1892.)

33. Kostenitsch, J. De l'évolution de la tuberculose provoquée chez les lapins par les bacille morts, etc. Arch. méd. Exp. d'Anat. Path., vol. v., No. 1, 1893.

34. Grancher, J., et Martin, H. Notes sur les vaccinations antituberculeuses. Congrès p. Tuberculose, 1891, 1896.

35. Grancher, J., et Ledoux-Lebard. Etudes sur la tuberculeux expérimentale du lapin. Arch. de méd. Exper. d'Anat. Path., No. 2, 1891.

36. Freudenreich, E. V. Ueber die toxische Wirkung der Cultur products den Hühnertuberculose. (Ref. Baumgarten's Jahresb., 1893.)

37. Masur, A., u. Kockel. Zur Kenntniss von der Wirkung todted Tuberkelbacillen. Ziegler's Beiträge, vol. xvi., 2, 1894.

38. Abel. (Injections of Dead Tubercle Bacilli.) Deutsch. med. Wochen., p. 482, 1892. (Ref. Masur u. Kockel.)

39. Carriére, G. Etudes expérimentales des altérations histologiques du foie et du rein produites par les toxines tuberculeuse (tuberculin). Arch. de méd. Exper. et d'Anat. Path., vol. ix., No. 1, January, 1897.

40. Sciolla. (Die toxine der Tuberculose.) VIII. Cong. Rome, October, 1896. (Abstr.) Hygienische Rundschau, vol. vi., No. 17, 1897.

41. Bâbes, V., u. Proca, G. Untersuchungen über die Wirkung der Tuberkelbacillen und über gegenwirkender Substanzen. Zeitsch. f. Hygien. u. Infekt., vol. xxiii., No. 3, 1896.

42. Uhlenhuth. Zur Kenntniss der giftigen Eigenschaften der Blutserums. Zeitsch. f. Hygiene u. Infekt., vol. xxvi., No. 3, 1897.

43. Behring, E. Ueber Heilprincipien, insbesondere über das aetiologische und des isopathische Heilprincip. Deutsch. med. Wochen., No. 5, 1898.

44. Kahler. Peptonurie nach Injektion des Koch'schen Mittels. Wien. klin. Wochen., No. 3, 1891.

45. Lenoir. (Albumoses in Urine of Tuberculous Patients.) Ref. Matthes. Progrès Méd., No. 30, 1893.

46. Maragliano. Le sérum antituberculeux et son antitoxine. Revue de la Tuberculose. No. 2, 1896.

ACUTE LEUKÆMIA.

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Since Virchow[1] first described the changes which occur in the blood of leukæmia this disease has generally been looked upon as essentially chronic in nature; a year usually elapses before all the typical symptoms which mark the disease occur, and at least another year passes before the case ends in death. In 1857 Friedreich[2] described a case which lasted but six weeks from the beginning of the symptoms until death. From that time until 1888 there were reported in the literature a number of cases, with a uniform symptom-complex and with uniform post-mortem lesions. These cases were collected in the now classical article by Wilhelm Ebstein,[3] entitled "Acute Leukæmie and Pseudo-leukæmie."

In the ten years which have elapsed since Ebstein's article was written there have appeared in the literature about three times as many such cases as were reported in the thirty previous years, Fränkel[4] alone having published abstracts of eleven cases. In 1897 Theodor[5] published the report of a case, together with the abstracts of forty-four other cases which had appeared up to that time. By a careful search of the literature we have been enabled both to add to this list and to correct it. Some of the cases published by Ebstein, and included in Theodor's list, were evidently instances of leucocytosis occurring in the course of other diseases. This error was made by Ebstein because it was not so well understood at the time he wrote as it is at present that a very marked leucocytosis may occur without the presence of the disease leukæmia. The gradual appreciation of this

[1] Virchow's Archiv, 1853, vol. v.
[2] Ibid., 1857, vol. xii.
[3] Deutsch. Arch. f. klin. Med., 1888–89, vol. xliv.
[4] A. Fränkel. Deutsch. med. Woch., 1895, and Verhandlung des Congress f. inn. Med., 1897.
[5] F. Theodor. Arch. f. Kinderheilkunde, 1897, vol. xx. p. 47.

latter fact caused Cabot,[1] in 1894, to write a thoughtful article suggesting that leukæmia was never an acute disease. Had he carefully read the reports of the cases published up to that time, however, he certainly would have been convinced of the reality of the disease.

The following cases are offered as throwing additional light on the question of acute leukæmia:

CASE I. (Fussell, Case 39 in series)—Mrs. G. M., English, aged thirty-seven years, married; has six healthy children living. Her father died of phthisis; her mother is living and well. Four brothers and three sisters are living and well; none dead. When young she had a tuberculous knee. She is the wife of a drunkard, and as such has had a slave's life, but otherwise has had no unusual hardships. At the time of onset she was nursing an eight months' old child. She was perfectly well (one of us having attended her in her two last labors) until six weeks before she came under observation. At that time she became weak, without pain, dyspnœa, palpitation of heart, or headache, but simply complaining of loss of appetite and weakness. She went to bed with fever and diarrhœa two and a half weeks before death. She then had a temperature of 101° in the morning and 103° in the evening. It ranged between these points until death. When first seen she was not unusually pale. Her urine contained albumin and casts. During the last week the albumin and casts became less, but the patient became very rapidly anæmic, with much dyspnœa, increasing and severe œdema, nausea, and repeated epistaxis.

Physical examination six weeks after the first symptoms and two and a half weeks after the first visit to her home. The heart-dulness was normal; there were soft systolic murmurs at the base and in the vessels of the neck. The lungs were resonant throughout, with no abnormal signs. The liver-dulness began at the fourth rib and extended to the umbilicus in the nipple line. The lower edge of the liver could be felt in the abdomen four fingers' breadth below the ribs, extending from the nipple around to the loin. The spleen could not be felt below the ribs; the dulness extended from the posterior axillary line to the nipple line and from the seventh rib to the margin of the ribs. The abdomen was extended; the skin was free from eruption. There was a slight spinal curvature to the right. The left knee was fixed and presented old healed sinuses. The submaxillary glands were enlarged, also the inguinal glands to a slight degree. The axillary glands could not be felt. Examination of the blood showed hæmoglobin, 32 per cent.; red corpuscles, 1,184,000, white corpuscles, 241,333 per c.mm.

Two days after the detailed examination there was much dyspnœa. Blood: red corpuscles, 1,273,400; white corpuscles, 362,500; hæmoglobin, 32 per cent. The temperature was normal for the first time in two weeks. There

[1] Cabot. Boston Med. and Surg. Journal, 1895.

were two bullæ, each the size of a pin-head, one upon the tip of the nose, the other upon the upper lip. The woman sank rapidly and died of asthenia.

The *autopsy* was performed eighteen hours after death. On the tip of the nose was a small gangrenous spot, and others over the abdomen. The lungs were crepitant, except at the apex of the left lung, which was infiltrated with a disseminated, apparently non-tubercular infiltration. There was a similar deposit in the apex of the lower left lobe, but none in the right lung. The thymus was not enlarged, and was apparently healthy. The heart was normal and both cavities were filled with huge chicken-fat clots. The spleen was rather soft, measured 6 x 4½ x 2 inches, and was of a dull purplish color. The liver extended far below the edge of the ribs, but weighed only four and one-half pounds. The apparent enlargement was due to an extension of the right lobe, the gall-bladder being seen in the middle of this lobe instead of at the edge. The gall-bladder was empty; the portal vein contained a large white clot. In the ileum Peyer's patches were much enlarged, with hard, raised, everted edges, and their centres ulcerated. Both kidneys were large, pale, and the seat of parenchymatous inflammation. The bone-marrow of the sternum, ribs, and tibiæ appeared *normal in color and consistency.*

This case is remarkable both from a clinical and a gross pathological view. No one seeing the case, with a continued fever for two weeks, a distended abdomen, diarrhœa, and nosebleed, would have considered it anything but one of typhoid fever. It was only when the remarkably rapid anæmia developed that a blood count was made, which showed the real nature of the case, and this was done rather as a routine matter than from a thought of any blood dyscrasia.

The blood: red cells, 1,273,000 per c.mm.
Leucocytes, 362,000 per c.mm.
Hæmoglobin, 32 per cent.

There was moderate poikilocytosis. The oligochromæmia was not marked. There were 2100 nucleated red cells per c.mm., nearly all normoblasts.

Differential count of leucocytes:
Polynuclear cells, 11 per cent. = 39,820 per c.mm.
Eosinophilic cells, 0.09 per cent. = 325 per c.mm.
Lymphocytes, 79.81 per cent. = 287,100 per c.mm.
Myelocytes, 5.54 per cent. = 20,275 per c.mm.
Degenerated cells, 4.00 per cent. = 14,450 per c.mm.

This case illustrates the point to which Fränkel has only recently assented, that the increase in the leucocytes need not be confined to the lymphocytes.

The eosinophiles alone in this case are absolutely normal in numbers. The polymorphonuclear cells present some degree of that polymorphism

which is a characteristic of leukæmia. The myelocytes were easily differentiated from the large lymphocytes by the presence of neutrophilic granulations. The lymphocytes are of widely varying size, the nuclei are usually pale and may be irregular; in some of the cells no protoplasm can be made out; none of these cells have granulations. The degenerated cells do not present their nuclear changes when treated by the ordinary methods; fixation by heat, followed by immersion in a solution of picric acid, is necessary to bring them out.

Microscopic examination. The leukæmic infiltrations are widespread, but not massive. In the spleen and lymph-glands the regular arrangement of trabeculæ, recticulated tissue, and lymph-cells is distorted; in areas the lymph-channels seem dilated. The spleen does not present an excess of pigment. Hemorrhages are rare in these tissues. In the *kidneys* are seen the most extensive infiltrations in this case. In the cortex particularly are large collections, which surround both the glomeruli and the tubules, and often penetrate the glomeruli. There is some arteritis. The renal cells are degenerated. In the *liver* the infiltrations are both interlobular and perivascular. The hepatic cells are less degenerated than the renal. In a few places the infiltrations may be seen penetrating the wall of a vein, thus agreeing with the findings of Benda; but there were no hemorrhages in these situations. The pancreas and adrenal bodies both exhibited moderate infiltration with parenchymatous degenerations. The lungs are generally infiltrated. In areas, however, there is consolidation, composed partly of leukæmic infiltration and partly of an exudate which reacts to the stains for fibrin and presents colonies of thick bacilli whose nature cannot be determined. The heart presents only slight infiltrations, and its muscle presents less degeneration than would be expected. In the alimentary tract there is more or less degeneration of the epithelium. In the small intestine are many ulcers, which are seen to be seated upon the summits of extensive lymphatic nodules, at the bases of which the infiltration extends into the submucosa. The lymphatic cells likewise form columns between the epithelial cells, and are seen here and there in the other coats of the intestine. The retroperitoneal glands are not in the least necrotic, and look like the other enlarged glands of the body. The bone-marrow of the ribs, sternum, and tibiæ presents a lymphatic overgrowth without any hyperplasia of the red cell-elements; in fact, red corpuscles are abnormally scarce in this marrow. The lymphatic cells are quite uniform in appearance, but only a few of them contain neutrophilic granulations (as noted in the smeared specimen of the fresh marrow). The infiltrations in general resemble closely the large lymphocytes. In some situations many degenerated cells are to be seen, and in all the viscera mononuclear cells with neutrophilic granulations (myelocytes) may be seen, although in very small numbers.

CASE II. (Jopson, Case 56 of series).—N. K., a white girl, aged fourteen years, was first seen July 14, 1897. The family history was negative. She had been complaining for a few weeks with pains in the knees, especially

the left. Examination showed no organic joint disease, and, except marked nervousness, amounting at times to hysteria, there were no general symptoms. The pains complained of were ascribed to hysterical mimicry, as the patient had been much in company of a sick child friend suffering from dropsy. There was no anæmia noticed at this time, and physical examination gave negative results. The menstruation was regular. The patient was seen occasionally during July. The nervous manifestations continued, and the patient was taken first to the seashore and later to the country. While in the country in the early part of August she became quite ill and a physician was called in. At this time she began to have what, from the accounts given, were intermittent febrile attacks. On August 24th she was again seen, and very marked anæmia was then apparent. The appetite was poor. There was the history of brief attacks of fever, but the nervous symptoms were less marked. A diagnosis of chlorosis was made, and she was ordered iron in the shape of Blaud's pill.

On August 28th she was seen at the office in the evening, having been taken to the Park in the afternoon; she was languid and disinclined to move about, but no great loss of strength had been observed until that date—an important point in view of the subsequent rapid course of the disease. Her temperature was 103.5°. There were painful enlargements of the submaxillary lymphatic glands on the right and of the sublingual on the left side. This had not been present when seen four days previously. She had also expectorated blood since the last visit. An examination of the throat showed entire absence of inflammation, but several spots of clotted blood were seen on the gums and pharynx. The exact site of the bleeding could not be determined. She appeared intensely anæmic. She was ordered to bed, placed upon a liquid diet and stimulating treatment, and the iron continued. Hot applications to the neck caused the painful swelling of the glands to subside within about twelve hours. The temperature gradually declined, reaching 99.5° in a few days.

Physical examination at that time showed a systolic murmur at the apex of the heart and venous pulsations in the neck. There were a few petechial spots on the skin, which had been observed for some days. There were no abdominal symptoms. The urine was normal. The expectoration of blood from the mouth continued in small amounts; there was no epistaxis. The nervous excitation returned as the patient's strength failed. On September 3d the blood was examined. The patient became partially comatose toward evening and died the same day, six days from the time she had taken to her bed. Owing to the absence of an early blood examination, the exact date of the onset of the disease cannot be fixed, but granting that it dated from the time she first came under observation, when it will be remembered there were no special signs of any blood disease, the duration was not over two months.

Blood-examination:

Erythrocytes, 800,000 per c.mm.
Leucocytes, 134,000 per c.mm.

Poikilocytosis is moderate. The color is moderately reduced. There are 4615 nucleated red cells in each c.mm., all normoblasts.

Differential count of leucocytes:

Polymorphous neutrophilic cells, 1.52 per cent. = 2040 per c.mm.
Lymphocytes, ungranulated, 94.32 per cent. = 126,485 per c.mm.
Degenerated cells, 4.16 per cent. = 5775 per c.mm.

Many of the larger mononuclear cells are clumped together, almost agglutinated. The neutrophilic granulations in the polynuclear cells are abnormally sparse. The number of polynuclear leucocytes is probably never under 3000 per c.mm. under normal conditions; in this case they are absolutely reduced, thus corresponding to the condition which Fränkel found in his cases. The above count was based upon a differential count of 5000 cells, and in that number not one eosinophilic granule was seen.[1] The degenerated cells seem to have been largely mononuclear. These changes were first well described by Gumprecht; they have since been found in all varieties of leukæmia. They are not, however, peculiar to it. The tremendous excess of the lymphocytes is better illustrated by the number than by the percentage. The size of these cells varies from that of the normal small lymphocyte up to one larger than the large mononuclear cell, 15 μ. The polymorphism, while not pronounced, is very evident.

Autopsy. This was performed twenty hours after death. There was not marked emaciation. The tissues generally seemed quite bloodless. The lungs appeared normal except for some œdema and hypostatic congestion. The heart-muscle was pale, and there were hemorrhages into it and underneath its serous coats. The liver was large, pale, and appeared fatty. The spleen was somewhat enlarged, hard, but not fibrous, and presented areas of hemorrhages. The kidneys were large, pale, and anæmic. The adrenal bodies appeared normal. The retroperitoneal and thoracic lymph-glands were moderately enlarged. The spinal cord was removed, but presented no signs of disease; the brain could not be removed. The stomach and intestines presented few changes; the follicles seemed slightly prominent; but there were no macroscopic ulcerations. No lymphomata were apparent in the organs. The marrow of the ribs and sternum was examined; it was soft, less fatty, and more cellular than normal, but not splenified.

Microscopic examination. The results are in brief as follows: There is universal lymphatic infiltration, not marked and rarely localized in nodes. In the heart-muscle the leucocytes lie between the muscle fibres and along the fibrous tissue; the muscle-cells are granular; their striations are obscured; here and there are areas of opacity which suggest hyaline degeneration. The liver is extensively infiltrated; in a few places we have been able to see the infiltration of the capillary walls described by Benda; the hepatic cells are moderately degenerated, the nuclei stain indistinctly, and occasionally present abnormal formations in the nuclear chromatin. The kidneys are less extensively infiltrated; the collections seem most marked in the cortex.

[1] In a few slides studied later, however, there are a notable number.

The renal cells are markedly degenerated; in some instances the glomeruli have become filled with leucocytes. In the adrenal bodies the infiltration is mostly in the peripheral layer. The cord presents very few infiltrations. Dr. Joseph Sailer has kindly informed us that with Nissl's stain no alterations are to be seen. The lymph-glands show a cellular hypertrophy. The regular reticulated arrangement of the trabeculæ is altered; the cellular overgrowth seems to have broken all boundaries. The same statement applies to the spleen, which is not abnormally pigmented. In all these situations the cells are of the same general character as those of the blood. In applying the triple stain to the organs we have been surprised to note the great scarcity of polynuclear cells; even in the spleen there are very few. We have never seen tissues so free from granulations. The bone-marrow examined is not markedly pyoid; there are areas of cellular overgrowth in which myelocytes are seen side by side with lymphocytes; the red cells are sparse, notably so. With reference to the hemorrhages, as a general thing they are seen in the infiltrated areas, but we have never been able to determine the break in the vessel, if such existed. In the alimentary tract the infiltration is moderate. The epithelium is degenerated, and in a few places are small erosions, really superficial ulcers.

The following abstracts include all the cases of which we can find traces published up to the present time (May, 1898), including the two of our own, comprising a total of fifty-six undoubted cases of acute leukæmia occurring in man, and one marked case occurring in a calf. The series includes also cases which have been published as acute pseudo-leukæmia; we have included them in this table because of their complete identity with the symptom-complex of acute leukæmia. There are scattered through the literature notes of several additional cases mentioned in discussions, but as there are no details given they are not included:

CASE 1.—Friedreich, *Virch. Arch.*, 1857, xii. p. 37. Female, aged forty-six years. *Duration.* Six weeks. *Symptoms.* Conjunctival hemorrhages; bleeding from genitals; spleen enlarged; glands very slightly swollen; diarrhœa after six weeks, with loss of appetite; enlargement of the liver; ulcer on the left side of the mouth; anæmia, weakness, œdema of the feet, severe bronchitis, temperature never raised. *Blood.* Not noted. *Post-mortem.* Leukæmic condition of large intestine, stomach, liver, and kidneys; infiltration of abdominal glands; marked ulceration of the small intestines, which resembled typhoid lesions in Peyer's patches and solitary follicles.

CASE 2.—Martin, *St. Barth. Hosp. Reports*, Sept. 1865, i. p. 268. Male, aged six and a half years. *Duration.* Ten weeks. *Symptoms.* Glands and spleen enlarged; stomatitis with ulcers; petechiæ general; gastric irritability; delirium; uric acid in urine. *Blood.* Large excess of whites. *Autopsy.* Con-

solidated spleen six by two and a half inches; lymph glands enlarged; internal hemorrhages.

CASE 3.—Immermann, *Deutsch. Arch. für klin. Med.*, 1874, xiii. p. 276. Female, aged seventeen years. *Duration.* Six weeks. *Symptoms.* Hemorrhage from the mouth; petechiæ over the general surface, swelling of glands, spleen increased 14–19 cm.; considerable vomiting, râles in the lungs; heart beat 126 to 132; pulsations in jugular vein; temperature from 37° to 40°; great tenderness over the bones. *Blood.* Increase of white cells 1–20, the white cells were mostly small, with a small amount of protoplasm; the blood was fluid and bright red; post mortem the blood was thin and resembled that of leukæmia. *Autopsy.* Much hemorrhage into the right retina; petechiæ in the skin; hyperplasia of the tonsils; spleen 15 x 12 x 2½ cm., with wrinkled capsule; enlargement and pigmentation of the solitary follicles and Peyer's patches; myocarditis; hyperplasia of the bone-marrow.

CASE 4.—Kelsch. *Arch. de Phys. norm. et path.*, Paris, 1875, vii. p. 492. Male, aged twenty-eight years. *Duration.* Six weeks. *Symptoms.* Had hemorrhages from lung and kidneys, nosebleed, numerous petechiæ over body; enlargement of all superficial glands; pulse is feeble; mucous râles in the lungs; bloody urine; temperature raised. *Blood.* Reds, 1,000,000; whites, 14,000. *Post-mortem.* Hemorrhages under the skin; enormous mass of lymphatic tissue in mediastinum; Peyer's patches and solitary follicles enlarged and infiltrated; lungs normal; heart, hemorrhages in the surface; myocarditis; kidneys contained microscopic lymphatic tumors; bone-marrow shows leukæmic infiltration; spleen weighs 350 gms., with enlargement of Malpighian bodies.

CASE 5.—Lowenstein, *Deutsch. Arch. für klin. Med.*, 1876, Bd. xviii. p. 120. Male, aged fifty-nine years. *Duration.* Three weeks. *Symptoms.* Hemorrhages not mentioned; lymph glands markedly enlarged, and numerous tumors over different parts of the body; gastric symptoms in beginning; some bronchitis; heart weak; urine contained much albumin; temperature from 38° to 39°; hemiplegia. *Blood.* Not examined during life; post mortem the blood from crural vein showed the red and white cells to be of equal number. *Post-mortem.* Hemorrhage into the brain; glands markedly swollen; spleen 17 x 12 x 7 cm.; leukæmic infiltration of intestine; lungs œdematous; myocarditis; kidneys infiltrated with lymphatic cells; bone-marrow of a yellow-gray color.

CASE 6.—B. Kussner, *Berlin. klin. Woch.*, 1876, N. 9, S. 109. Female, aged forty-six years. *Duration.* Sixteen days. *Symptoms.* Petechiæ all over the body; bleeding from hemorrhoids; ecchymosis in gums; redness of palate; some nosebleed; enlarged parotid; splenic region painful, spleen could be felt; lungs and heart normal; urine contained a small amount of albumin; temperature 40°. *Blood.* White cells were increased and mostly large and polynuclear with many transitional forms. *Post-mortem.* Hemorrhage into lungs; spleen 10 x 20 x 5 cm.; excrescences on surface; follicles not very prominent; bone-marrow a yellowish-green.

CASE 7.—Ponfick, *Virch. Arch.*, 1876, Bd. lxvii. S. 369. Male, aged nineteen years. *Duration.* Five weeks. *Symptoms.* No hemorrhage noted; glands rapidly enlarged; liver and spleen enlarged three weeks after beginning of disease; swelling of the tonsils, gangrene of the lips; high fever; temperature 40°. *Blood.* White cells increased, 1 white, 2 reds. *Post-mortem.* Spleen was enlarged 20 x 8 x 5 cm., follicles enlarged; enlargement of follicles of tongue and tonsils; some liquid in pleural cavity; myocarditis; leukæmic nodes in both kidneys; hemorrhagic pseudo-membranous colitis; leukæmic liver; marked hyperplasia of the bone-marrow.

CASE 8.—Keating, *Amer. Journ. of Obstetrics*, 1886. Male, aged four and a half years. *Duration.* Nine weeks. *Symptoms.* Petechiæ all over the body; epistaxis; enlargement of cervical glands, which gradually increased; rapidly increasing anæmia; enlargement of spleen; high fever. *Blood.* Three hours after withdrawal: red corpuscles not changed; white greatly increased in number, 50 to 60 in each field, No. 7 Hartnack; variable in size; many are small, not more than one-third size of larger form; they resemble the small colorless cells which Virchow has noted as present in lymphatic leukæmia. *Post-mortem.* None.

CASE 9.—Litten, *Berliner klin. Woch.*, 1877, N. 19, S. 256. Female, adult. *Duration.* Five weeks. *Symptoms.* Severe anæmia; hemorrhage into the retina; the glands were not enlarged, neither was the spleen nor liver enlarged; marked vomiting; weak heart; was nursing a child. *Blood.* At first the red cells were diminished and the white only slightly increased; the whites were large without a nucleus (sic); later the whites rapidly increased; 1 white to 15 reds; at this time the whites were round, moderately large, and contained a large nucleus with only a small amount of granular protoplasm, some were polynuclear; before death 1 white to 4 reds. *Post-mortem.* Hemorrhage in retina; liver anæmic, otherwise normal; glands were not enlarged; myocarditis; leukæmic nodes in kidneys; spleen 12 x 8 x 3, grayish-red, enlarged follicles; bone-marrow greenish-yellow, soft, with large leukæmic nodes.

CASE 10.—J. Englisch, *Jahresbericht über die Leistungen und Forschungen in der geoammatem Medicin*, 1877, xii., Bd. ii. S. 255. Male, aged twenty-four years. *Duration.* Twelve days. *Symptoms.* Eight days after working in cold water patient was seized with pain in the ankles; no hemorrhages; at first the spleen, liver, and glands were normal; incision was made over the painful spot in tibia, and showed thickened periosteum; death occurred four days afterward, preceded by fever, enlargement of spleen, and cerebral symptoms. *Blood.* The relation of white to red cells 1 to 3. *Post-mortem.* Basilar meningitis; endocarditis, pericarditis; enlargement of liver and spleen, with lymphoid infiltration; hyperplasia of bone-marrow of all bones.

CASE 11.—C. Zumpe, *Der Heilk.*, Leipsic, 1878, Bd. xix. S. 473. Aged fifteen and three-quarters years. *Duration.* Seven weeks. *Symptoms.* Family history of tuberculosis; patient always well; began with weakness; in beginning spleen not large; hemorrhage; petechiæ in tongue and neck, nose-

bleed; glands and tonsils large; spleen began to enlarge in a few days and soon reached 9½ x 18 cm., three fingers below the ribs; loss of appetite; heart and lungs comparatively normal; bloody urine; moderately high fever. *Blood.* Increase of white, reds to white 1 to 1; whites the same size as the red. *Post-mortem.* Petechiæ over the skin; spleen three-fingers' breadth below the ribs; bloody serous fluid in the pleural cavity; heart soft; liver contained lymphatic nodes; glands were not swollen, and microscopically were not changed, except the follicles were filled with round cells.

CASE 12.—A. Fränkel, *Ztschr. für klin. Med.*, 1881, Bd. cxi. S. 405. Male, aged eighteen years. *Duration.* Twenty days. *Symptoms.* Patient always well except always subject to nosebleed; the patient began with nosebleed which could not be controlled; on examination enlargement of lymph glands all over the body; spleen could be felt 2 cm. below the ribs; heart and lungs negative; temperature normal; paralysis of left face, arm, and neck. *Blood.* Marked increase of white cells; whites were about the size of reds and had a large nucleus, the large nuclears were very infrequent. *Post-mortem.* Enlargement of glands all over body; spleen about twice the normal size, with enlarged follicles; the Peyer's patches were swollen; ulcers in the cæcum; hemorrhage into the brain; degeneration of the bone-marrow.

CASE 13.—Gaucher, *Le Progrès Méd.*, Paris, 1881, xxiii. p. 445. Male, aged thirty-eight years. *Duration.* Nine weeks. *Symptoms.* Syphilitic skin disease; disease began with symptoms of grippe; hemorrhages all over the skin; epistaxis; enlarged glands all over body; spleen extends to umbilicus; liver not enlarged; dulness at base of left lung; there was considerable diarrhœa; much fever; on the eighth day of observation the spleen reached the umbilicus. *Blood.* One white to 16 reds; just before death the red cells 2,800,000. *Post-mortem.* Old pericarditis; spleen enlarged and sclerosed; Peyer's patches not hypertrophic; some enlargement of the mesenteric glands; lungs contained lymph nodes; lymphomata in front of mediastinum.

CASE 14.—Wadham, *The Lancet*, Jan. 26, 1884, p. 158. Male, aged five and a half years. *Duration.* Eight weeks. *Symptoms.* Good family history; had a severe fright; began with pain, cough, constipation, sleeplessness; hemorrhage not observed; glands of neck enlarged; spleen could not be felt; the gums were soft; temperature from 100° to 102°. *Blood.* Blood before death contained 3 whites to 1 red (sic). *Post-mortem.* Petechiæ in all the organs; none on the surface of the body; mesenteric glands enlarged; liver pale, studded with whitish nodules; spleen contained infarcts of yellowish color; hemorrhage in retina.

CASE 15.—J. H. Musser, *Trans. Philada. Co. Med. Soc.*, Sept. 28, 1887. Male, aged eleven years. *Duration.* Five weeks. *Symptoms.* Began with fever, swelling in parotid region and enlargement of all the glands; very anæmic; splenic dulness markedly increased; herpes on the face; blood-stained mucous expectoration. *Blood.* Reds 3,700,000, white to red 1–40; just before death, reds 2,100,000, whites to red 1–40. *Post-mortem.* None.

CASE 16.—Wilhelm Ebstein, *Deutsches Arch. für klin. Med.*, 1888–89, xliv.

p. 343. Male, aged twenty-three years. *Duration.* Four weeks. *Symptoms.* Headache and loss of appetite; hemorrhages all over the skin, nosebleed; mucous membrane of mouth pale, spleen enlarged; temperature 37° to 38°; bloody stool; bleeding from gums. *Blood.* Red 3,273,000, whites 165,650. *Post-mortem.* Swelling of all the glands; enlargement of spleen; lymphadenoma in kidneys, necrosis of epiglottis, swelling of follicles of intestine.

CASE 17.—Mosler, *Virch. Arch.*, 1888, cxiv. p. 461. Reported as a case of pseudo-leukæmia. Male, aged fourteen years. *Duration.* Eight weeks. *Symptoms.* Enlargement of glands in both axillæ and in neck; no increase of spleen or liver; temperature 38°; injections of arsenic were given followed by enlargement of the spleen, fever, exudation on the tonsils, death; petechiæ over body; hæmatemesis; bloody urine. *Blood.* At first there was no increase of white cells; later there was a marked increase of the white cells. *Post-mortem.* None.

CASE 18.—Westphal, *Münchener med. Woch.*, 1890, No. 1. Male, aged sixteen years. *Duration.* Four weeks. *Symptoms.* Had a fall one year before, and was never strong afterward; hemorrhage into retina; rapid anæmia; petechiæ over skin and in mouth; swelling of the glands; splenic tumor; gangrenous exudation on the tonsils; death from puncture of spleen. *Blood.* Reds 816,000, whites 24,000, 45 per cent. hæmoglobin; the white cells mostly small; no eosinophiles. *Post-mortem.* Some hemorrhage into brain; no hemorrhage over body; lymph glands enlarged; spleen enlarged; liver filled with small cells; infiltration of bone-marrow.

CASE 19.—Hans Leyden, *Dis. Beitrag zur Lehre von der acuten Leukämie*, Berlin, 1890. Male, aged twenty-five years. *Duration.* Forty-one days. *Symptoms.* Headache, chills, pains in legs, back, and in splenic regions; anæmic; glands enlarged; spleen enlarged very rapidly, painful; œdema; fever 38° to 39°. *Blood.* At first reds 2,200,000, whites 400,000; large number of mono- and polynuclear cells; then reds 1,450,000, whites 500,000; later reds 1,130,000, whites 360,000. *Post-mortem.* Large spleen, 2270 cms., 32 x 16 x 9; old infarcts, soft and brown; Peyer's patches and solitary follicles hyperplastic; pleural effusion; dark-red marrow; lymph glands enlarged; microscopically infiltration of all tissues.

CASE 20.—Obrastzow, *Deutsch. med. Woch.*, 1890, vol. xvi. p. 450. Male, aged seventeen weeks. *Duration.* Four weeks. *Symptoms.* Nosebleed, petechiæ, mucous membrane pale, enlargement of glands, spleen rapidly enlarged; temperature 38° to 40°. *Blood.* First examination, white cells slightly increased; second examination, marked increase of white cells, small, finely granular, containing a round nucleus; whites to reds, 1 to 7; hæmoglobin, 30 per cent. *Post-mortem.* Bloody serum in pleural cavity, ecchymosis in peritoneum; lymphomata in various parts of chest wall; all glands enlarged; leukæmic infiltration of liver, spleen enlarged.

CASE 21.—Obrastzow, ibid. Male, aged thirty-two years. *Duration.* Twelve days. *Symptoms.* Petechiæ all over body; this patient had treated a case of acute leukæmia and was taken sick about a month afterward;

swelling of gums; enlargement of glands and rapid enlargement of spleen, 37–38½. *Blood.* Whites were increased, finely granular, containing a round nucleus; whites to reds, 1 to 9.

CASE 22.—Hinterberger, *Deutsch. Arch. für klin. Med.*, 1891–92, xlviii. p. 324. Female, aged thirty years. *Duration.* Three weeks. *Symptoms.* Always well before the attack; cutaneous hemorrhages all over the body; enlargement of spleen; swelling of glands, swelling of gums; temperature 38° to 39½°. *Blood.* Whites to reds, 1 to 7. *Post-mortem.* Liver enlarged; solitary follicles and Peyer's patches were enlarged.

CASE 23.—Fuchs, *Acute und chronische Leukämie*, 1891 (Dissertation). Male, aged eighteen years. *Duration.* Seven weeks. *Symptoms.* Œdema; fever, petechiæ, nosebleed, swelling of glands, coma; spleen moderately enlarged. *Blood.* At first no change in blood, 1 white to 50 reds before death. *Post-mortem.* Stomach dilated; blood in peritoneum, liver large, fluid in pleural cavity; internal ecchymosis; spleen 18 x 12½ x 4; dark follicles and Peyer's patches enlarged.

CASE 24.—Guttman, *Berl. klin. Woch.*, 1891, vol. xxvi. Male, aged twenty-one years. *Duration.* Two weeks. *Symptoms.* Both tonsils removed for adenoids; petechiæ all over body, nosebleed, bleeding from mouth; liver enlarged, spleen enlarged; no fever. *Blood.* Whites to reds, 1 to $1\frac{4}{10}$; only a few polynuclear and eosinophile cells. *Post-mortem.* Large subcutaneous hemorrhages; hemorrhage in brain; thymus much enlarged; spleen three times as large as normal; bone-marrow dark red.

CASE 25.—Wertheim, *Zeitschrift für Heilkunde als Forlaetzung der Prager. Vierteljareschrift für praktische Heilkunde*, 1891, Bd. xii., Fall 7, S. 282. Female, aged fifteen years. *Duration.* Six weeks. *Symptoms.* Always well previously; cough and shortness of breath; petechiæ over the skin; hæmoptysis; lymph glands not enlarged; spleen could not be felt; no pain in bones; temperature 38.8°. *Blood.* Marked increase of white cells. *Post-mortem.* Spleen weighed 500 gms.; swelling of glands, exudation on tonsils; infiltration of epiglottis.

CASE 26.—Litten, *Verhandlungen des Congress f. innere Med.*, 1892, S. 165. *Duration.* Three and a half days. *Symptoms.* Bronchial catarrh; on first day spleen not enlarged, on second day could be felt; hemorrhage in retina; bleeding from ear; second day of disease, spleen larger; petechiæ. *Blood.* Showed whites 1, reds 9; whites were large, with large nuclei and appeared to be undergoing fatty degeneration.

CASE 27.—Traversa, *La Riforma Medica*, 1893, vol. iii., No. 3, p. 26. Reported as pseudo-leukæmia. Male, aged seventy-one years. *Duration.* Ten weeks. *Symptoms.* Enlarged inguinal glands, irregular fever, tonsils enlarged, spleen enlarged, diarrhœa, ecchymosis. *Blood.* Whites 24,800, reds 4,827,000; later 3,218,000 reds, 53,600 whites, 40 per cent. hæmoglobin; streptococci in blood. *Post-mortem.* Lymph glands and spleen enlarged, purpura over body.

CASE 28.—Eichhorst, *Virch. Arch.*, 1892, Bd. cxxx. S. 367. Male, aged

eight years. *Duration.* Fourteen days. *Symptoms.* Always well previously; vomiting of blood; rapid failure of strength; bleeding from mucous membrane of mouth; enlargement of liver; spleen extended almost to navel; lungs normal, urine normal; temperature 38.5°. *Blood.* 1,000,000 red corpuscles, 88,000 white cells, 25 per cent. hæmoglobin; no nucleated reds; white cells about the size of the reds, and contain 2 to 4 nuclei; no eosinophiles found. *Post-mortem.* Spleen 15 x 18½ x 3½; capsule smooth; trabeculæ prominent; lymph glands in hilus of spleen enlarged, also about pancreas; ulcers in stomach; mesenteric glands enlarged; hydrothorax; fatty degeneration of heart; no disease of bone-marrow.

CASE 29.—Nobel, *Deutsche medizinal Zeitung*, 1892, No. 100, p. 1176. Sex not given; aged forty years. *Duration.* Ten days. *Symptoms.* Hemorrhage on skin, gangrenous stomatitis, softening of gums, swelling of glands, spleen and liver swollen; temperature 37.2° to 39.2°; urine contained uric acid and albumin. *Blood.* Whites to reds, 1 to 20; increase of myelocytes with mitosis; nucleated reds. *Post-mortem.* Spleen much enlarged; liver much enlarged; leukæmic infiltration of kidneys; lymphoid degeneration of bone-marrow.

CASE 30.—Nobel, ibid. Female, aged thirty years. *Duration.* Twenty-one days. *Symptoms.* Hemorrhage; stomatitis; clinical picture of morbus Werlhofii. *Blood.* One white to 50 red; increase of myelocytes with mitosis; nucleated reds. *Post-mortem.* Same as Case 29; also lymphatic change in thymus.

CASE 31.—Greiwe, *Berlin. klin. Woch.*, 1892, Bd. xxix. p. 825. Male, aged twenty-eight years. *Duration.* Eleven days. *Symptoms.* No hereditary disease; had a fall a short time before disease began; sudden hemorrhage from nose; subcutaneous hemorrhages; gums soft, swollen, and bleeding; lymph glands enlarged, spleen enlarged. *Blood.* Increase of large mononuclear cells, with a few polynuclear cells and eosinophiles. *Post-mortem.* Bloody fluid in pericardium; infiltration of liver with small cells; spleen soft and enlarged; bone-marrow pale.

CASE 32.—Dreschfeld, *British Med. Journ.*, 1892, Part I., p. 893. Reported as pseudo-leukæmia. Male, aged twenty-three years. *Duration.* Six weeks. *Symptoms.* Always well; spleen slightly enlarged; lymphatic mass under sternum; fever. *Blood.* Whites 1 to 40, small, mononuclear; a few eosinophile cells; a few large mononuclear cells. *Post-mortem.* Infarcts of spleen, kidneys, and liver; no change in bone.

CASE 33.—Hilbert, *Deutsche med. Woch.*, 1893, vol. xix. p. 875; also Kirstein in inaugural thesis. Female, aged thirty-seven years. *Duration.* Seven weeks. *Symptoms.* Pain in abdomen; anorexia; cough; pregnant eight months; bleeding from gums; petechiæ all over body; bronchial catarrh; retinitis (leukæmic); temperature 38°; infiltration of gums and ulceration of gums; glands enlarged, spleen and liver not enlarged; died after giving birth to a dead child. *Blood.* Increase of white cells one week before death, a few nucleated reds, pale mononuclear leucocytes in great number, polynuclear cells, a few eosinophiles. *Post-mortem.* Swelling of Peyer's patches and soli-

tary follicles; ulcerations in large intestine; spleen and glands only slightly enlarged; lymphatic bone-marrow (both red and white); hemorrhage in organs.

CASE 34.—Hintze, *Deutsche Arch. für klin. Med.*, 1894, liii. p. 377. Male, aged sixteen years. *Duration.* Seven weeks. *Symptoms.* Petechiæ all over body; pain in ankles; sweats; spleen rapidly enlarged; general glandular swelling; mucous membrane of mouth as in scurvy; toward death spleen and liver increased in size. *Blood.* Increase of white cells, mostly large, mononuclear, with small amount of protoplasm; few with indented or multiple nuclei; few eosinophiles. *Post-mortem.* Lymphatics enlarged; spleen enlarged, smooth, and infiltrated, dark red; liver and kidneys enlarged; Peyer's patches not enlarged; sternal marrow normal; cocci in organs; cells in liver, kidney, and glands.

CASE 35.—Ebstein, *Deutsche med. Woch.*, July, 1894. Reported as traumatic leukæmia. Male, aged thirty-six years. *Duration.* Six weeks. *Symptoms.* Well before an injury; hemorrhage under skin and from anus; swelling of inguinal glands, also in groins and neck; spleen markedly enlarged. *Blood.* Marked increase of white cells.

CASE 36.—Seeling, *Deutsche Archiv für klin. Med.*, 1895, vol. liv. p. 537. Male, aged eleven years. *Duration.* Three weeks. *Symptoms.* Scarlet fever accompanied by nephritis several years before; frequent examination showed only nephritis; suddenly petechiæ; swelling of gums; pain in bones; glands enlarged, spleen enlarged. *Blood.* Marked increase of white cells; large myelocytes with mitoses, a few lymphocytes and fewer polynuclear cells; post mortem the blood contained small single lymphocytes with one nucleus, while the myelocytes were few. *Post-mortem.* Ecchymosis in pleura; enlarged lymph follicles in stomach; Peyer's patches and solitary follicles enlarged; lymphatic infarcts in kidneys; glands enlarged, spleen enlarged.

CASE 37.—Müller, *Jahrbuch für Kinderheilkunde*, 1895, Bd. xliii. S. 130–148. Male, aged four years. *Duration.* Four weeks. *Symptoms.* Inflammation of brain nine months before; since, restless, nosebleed, no tenderness over bones; enlargement of glands, spleen greatly enlarged; small tumors in skin; bloody stools; diphtheritic exudation in throat; temperature 40.8°. *Blood.* Whites to reds as 1 to 13, 45 per cent. hæmoglobin; organisms in blood resembling those in exudate in throat; first group, mononuclear whites most numerous; larger than reds; then a large cell with irregular nucleus; second group, small lymphocytes size of reds, with nucleus rich in chromatin; third group, Ehrlich's polynuclear forms very scarce; a very few eosinophiles, 1011 in first group, 143 in second group, 30 in third group. *Post-mortem.* Petechiæ over body; myocarditis; spleen enlarged, dark and red; diphtheritic exudation in intestines.

CASE 38.—Müller, ibid. Male, aged four years. *Duration.* Four weeks. *Symptoms.* Patient had measles; pain over body; petechiæ and large subcutaneous hemorrhages(?); lymph glands enlarged, spleen swollen; temperature 38.4°. *Blood.* Whites to reds 1 to 11½ or 1 to 12; 951 large mononuclear, 171 lymphocytes; reds normal.

CASE 39.—Fussell and Taylor, *Univ. Med. Mag.*, 1895–96, p. 957. Preliminary report. Female, aged thirty-seven years. *Duration.* Six weeks. *Symptoms.* Always perfectly well; nursing at present time; severe nosebleed, swelling of glands of jaw; splenic dulness increased, spleen could be felt; liver felt below edge of ribs; diarrhœa, fever, nephritis; case resembled one of typhoid fever. *Blood.* Reds 1,184,000, whites 241,333; the red corpuscles were pale, a few nucleated reds; differential count of leucocytes gave polynuclear leucocytes 15 per cent., large mononuclear in transitional forms 14 per cent.; the large mononuclear were pale, with large nuclei, often situated near the margin of the cells, resembling the Fränkel cells; the other leucocytes were as small as lymphocytes and had no appearance of having come from the marrow. *Post-mortem.* Gangrenous spot on nose; spleen soft, 6 x 4½ inches, of a dull-purplish color; Peyer's patches were enlarged and ulcerated, with everted edges.

CASES 40 to 48 inclusive.—A Fränkel, *Deutsche med. Woch.*, 1895, vol. xxxi. p. 639. Both sexes, ages ranging from thirteen to thirty-four years. *Duration.* From twenty days to sixteen weeks. *Symptoms.* Cases began with feeling of weakness in previous healthy individuals; œdema; anæmia; hemorrhage from mucous membrane and in skin; parenchymatous hemorrhage into organs; glands enlarged, spleen swollen, and in most a palpable tumor; delirium, stupor; did not observe typhoid state; temperature usually raised. *Blood.* Condition of blood allows a diagnosis to be made on this one point alone; there is a characteristic increase of mononuclear elements; they belong to the category of lymphocytes; they vary in size from that of a red cell to one double its size; contain a large round or oval nucleus poor in chromatin; they do not contain eosinophile granulations; there is an actual reduction of the polynuclear cells; in two cases the whites disappeared before death. *Post-mortem.* The greatest number of the cells are found in the lymph glands—are found in all tissues, but are most numerous in the lymph glands.

CASE 49.—Robins and Argus, *Montreal Med. Journ.*, 1896–97, vol. xxv. Reported as pseudo-leukæmia. Male, aged nineteen years. *Duration.* Eight weeks. *Symptoms.* Weak, dull, pale, loss of flesh; hemorrhages over body; bronchial glands enlarged, spleen felt; temperature 102½° to 106°; liver felt; loss of appetite. *Blood.* Varied; at first whites normal, then rose to 66,000, then fell to almost normal; almost all lymphocytes.

CASE 50.—Goldschmidt, *Münch. med. Woch.*, 1896, No. 30. Male, aged two and a half years. *Duration.* Two months. *Symptoms.* Tonsils red and swollen; swelling of glands; slight enlargement of spleen; liver enlarged; urine contained albumin; œdema of face. *Blood.* Exquisite picture of leukæmic blood. *Post-mortem.* Swelling of glands; spleen 20 x 14 x 4; blue-red color.

CASE 51.—Theodor, *Arch. für Kinderheilkunde*, 1897, xxii. p. 47. Male, aged four years. *Duration.* Seven weeks. *Symptoms.* Always well until fall from horse; fall followed by bleeding from nose; hemorrhages all over body; all glands enlarged, spleen enlarged; temperature 38°. *Blood.* Whites 1,

reds 9; almost all small cells with nucleus colored intensely blue, and with a small amount of protoplasm (lymphocytes); there are a few large mononuclear cells, with large, slightly colored nuclei; only a few polynuclear and eosinophile cells; reds about normal.

CASE 52.—Herrick, *Journ. Amer. Med. Assoc*, 29, 1897, xi. p. 171. Male, aged twenty-seven years. *Duration.* Eight weeks. *Symptoms.* Excessive user of alcohol; enlargement of glands; anæmia; ulcer in mouth; gums bleeding; fever. *Blood.* Red cells vary but little; numerous nucleated red cells; white cells mostly correspond in every particular to common small lymphocytes; 98 large mononuclear forms, 9 polynuclear, 2 eosinophile cells, 23 large mononuclear with a wide rim of protoplasm.

CASE 53.—Fränkel, *Verhandlungen des Congress für inn. Med.*, 1897, 15. Male, aged thirty-one years. *Duration.* Two weeks. *Symptoms* No previous history; many petechiæ; no retinal hemorrhages; exudation in throat; enlargement of glands, spleen, and liver; paralysis of right side of face; fever. *Blood.* Reds 2,945,840, whites 31,250; hæmoglobin 55 per cent.; whites almost all lymphocytes, mononuclear, double the size of reds; also small lymphocytes, no neutrophiles; polynuclear almost all disappeared; a few eosinophiles; a few nucleated reds. *Post-mortem.* Hemorrhage in stomach and intestines; enlargement of Peyer's patches and solitary follicles; tumor under sternum; both tonsils much swollen; maxillary and cervical glands swollen; spleen 12 x 19; bone-marrow red; hemorrhage in sheath of facial nerve.

CASE 54.—Thomson and Ewing, *N. Y. Med. Rec.*, 1898, liii. p. 333. Female, aged twenty-one years. *Duration.* Eight weeks. *Symptoms.* Weak for seven months; sore-throat; arm swollen, red, and painful three weeks; pains in limbs; glands not enlarged; one ecchymosis; spleen just palpable. *Blood.* Reds 1,290,000, whites under 155,000; lymphocytes 33 per cent., myelocytes 12 per cent., polynuclear 5.5. *Post-mortem.* Ecchymosis in stomach; deposits in liver, marrow, spleen, and glands; spleen moderately enlarged; no lymph changes in alimentary tract.

CASE 55.—Stair, *Journ. Amer. Med. Assoc.*, 1885, iv. p. 586. Male, aged twenty years. *Duration.* Seven weeks. *Symptoms.* Spleen and glands enlarged rapidly; epistaxis. *Blood.* Reds 1 to whites 30.

CASE 56.—John Jopson. Not previously published. Female, aged fourteen years. *Duration.* Seven weeks. *Symptoms.* Pains in knees; anæmic; nervous; feverish at intervals; temperature 103½°; swelling of submaxillary and subinguinal glands; expectoration of blood; anæmia; urine normal; glands decreased; petechiæ; coma and delirium. *Blood.* Reds 800,000, whites 135,000. *Post-mortem.* Tissues bloodless; hemorrhage in organs; leukæmic infiltrations; myocarditis; liver large, leukæmic infiltration; spleen large, hard, simple hyperplasia; kidneys, leukæmic infiltration with nephritis; intestines, ulcerations in ileum, in solitary follicles; bone-marrow, lymphoid infiltration.

Wolff, *Thierartliche Woch.*, 1892. Calf. *Symptoms.* Swelling of all glands, especially in parotid region, giving appearance as though head were set in a

mass; failure of strength; enlargement of liver and spleen. *Blood.* During life 1 red to 13 whites, after death 1 white to 11 reds; lymphocytes 93 per cent., polynuclear cells 2 per cent., eosinophiles ¼ per cent.; cells with large single nucleus 5 per cent.; the lymphocytes were large white cells with large round or oval nuclei. *Post-mortem.* Swelling of Peyer's patches and necrotic areas in cæcum.

The analysis[1] of the abstracts shows the following facts:

Age. Nine cases occurred below the age of ten years; 13 cases occurred between the ages of ten and twenty years; 10 cases occurred between the ages of twenty and thirty years; 7 cases occurred between the ages of thirty and forty years; 5 cases occurred over the age of forty years.

The youngest subject was two and one-half years; the oldest, seventy-one years. It will be seen that the greatest number of cases occurred between the ages of ten and thirty years.

Sex. Thirty-three cases occurred in males; 12 cases occurred in females. In 2 the sex was not mentioned. In Fränkel's group both males and females occurred.

Duration. The cases lasted, from the beginning of the first symptom until death, from three and one-half days to sixty-three days, the average duration being approximately thirty-nine days. In one of Fränkel's cases the duration was about four months, but all the symptoms of the acute disease were present.

Predisposing Causes. No cause can be given for this most distressing malady. The patients came from all ranks of life. In several cases an injury received a greater or shorter time before the beginning of the disease was looked upon as the predisposing cause, but it occurred too infrequently to be of any moment. In one case—a most suggestive one (No. 21)—the patient had just previously nursed a leukæmic patient and examined his blood and urine. This is the only case in the series, however, in which contagion could be suggested.

Symptoms. Hemorrhage occurred in 39 cases. This usually was in the form of petechiæ, though large subcutaneous bleeding occurred. Nose bleedand hemorrhages from the mouth and other mucous membranes were common.

Lymphatic Enlargement. This occurred in 47 cases. Usually

[1] The analysis does not include Fränkel's cases published in Deutsch. med. Woch. for 1895.

this symptom was seen during life, but occasionally it was not discovered until the autopsy.

Enlargement of the Spleen. This occurred in 40 cases. This enlargement was seldom great, but in some cases the organ enlarged rapidly while the patient was under observation.

Pain over the Bones. This was quite a frequent symptom noted. It was most marked over the sternum and the bones of the legs.

Digestive Disturbances. There were frequently diarrhœa and vomiting, sometimes bloody stools and hæmatemesis. The mouth and pharynx were frequently the seat of ulcerations, sometimes of gangrenous lesions; the gums were often soft and bleeding.

Exudation upon the Tonsils. This occurred frequently enough to make it a notable symptom. The membrane was diphtheritic in appearance. As most of the cases occurred before the discovery of the Klebs-Löffler bacillus, this organism was not especially sought for, but no organism resembling it was described.

Temperature. In 31 cases there was a rise of temperature. In some of the cases—notably the two presented by ourselves—the fever was a very marked symptom, in the first case resembling closely typhoid fever; in other cases it varied greatly, and in some was septic in type.

Circulation and Cardiac Symptoms. There were no cardiac disturbances apart from those due to the increasing and rapidly fatal anæmia.

Respiratory Symptoms. Bronchial catarrh was quite a constant symptom, but seemed to have no especial diagnostic value.

Renal Symptoms. There was an increase in uric acid in most of the cases examined for it. Nephritis rarely occurred. Hæmaturia was present in several cases as a part of the blood dyscrasia.

Nervous Symptoms. In several cases there was hemiplegia, due to apoplexy. In other cases the symptoms were those belonging to any exhaustive disease.

Changes in the Blood. In the earlier cases the sole alteration noted was a marked increase in the number of leucocytes. Our present nomenclature was not then employed, but from the descriptions given in most of the earlier cases the mononuclear cells were those most notably increased. The later cases have naturally been better studied. As a rule, the red cells are markedly reduced, usually

below 3,500,000, often below 2,000,000, occasionally below 1,000,000 per c.mm. The alterations in the red cells have not been as marked as in chronic leukæmia and pernicious anæmia of like corpuscular reduction. Poikilocytosis has not been marked as a rule, microcytes have not been especially commented upon, macrocytes have not been conspicuous. Nucleated red cells have been rare in contrast to chronic leukæmia, while gigantoblasts have been but rarely noted. It seems that the bone-marrow does not undergo the compensatory hypertrophy seen in the more chronic anæmias. The number of the plaques seems to have attracted no attention.

The leucocytosis is usually moderate, often being below 100,000, and but once up to 500,000 per c.mm. In a notable number of cases the excess disappeared just before death. The cases have been essentially lymphatic in type and usually pure. A marked polymorphism in the size and shape of the lymphocytes has usually been noted; they are usually larger than red cells, are intensely or palely or unevenly stained; the protoplasm has commonly been described as small in amount and ungranulated; the nuclear chromatin has most often been described as similar to that of the large mononuclear cell, the large lymphocyte. We believe that Fränkel has demonstrated these cells to be true lymphocytes, and that the differences between them and the myelocytes are unmistakable. While this has been the usual type, it has not been the sole type, as originally claimed by Fränkel, who maintained that acute leukæmia always presented the one striking blood-picture which was alone diagnostic. Fränkel has recently receded from this position, and now admits that the blood-picture may be varied. Usually the polynuclear cells are not increased or have indeed been decreased; in a few cases they have been notably increased. The eosinophilic cells have usually been reported as very scanty; rarely they have been increased. In a few cases typical myelocytes have been present, in three cases only to any great extent. In the later reports mention has several times been made of degenerations in the white cells, affecting chiefly the nuclei. Fränkel and Benda,[1] who have done the most careful work on acute leukæmia, conceive the disease to be the result of an abnormal activity of the lymphatic tissue, not only in the lymph-glands, but universally

[1] Verhandl. d. Cong. f. Trans. Med., 1897, xv.

throughout the body, and especially in the bone-marrow. The blood-picture of acute leukæmia may occur in chronic leukæmia (case of Grawitz), but the pathological conditions in the tissues of these cases do not coincide with those seen in chronic lymphatic leukæmia.

Morbid Anatomy. The pathological conditions have been well studied only within the last few years. The lymph-glands, spleen, bone-marrow, liver, kidneys, and alimentary tract seem constantly affected. In none of the cases have any of these tissues been shown by careful study to have been free from alterations. The changes may be grouped into three divisions: lymphatic, hemorrhagic, and parenchymatous.

The lymphatic enlargements and infiltrations are not massive, as a rule. In the alimentary tract, however, they have often been very extensive, in consideration of the duration of the disease. The hyperplasia consists in cells of the same nature as those noted in the blood, lymphocytes of varying size and polymorphic in quality. In the mouth and in the intestines these collections frequently ulcerate; this is likely not a specific process; the tissue is of low vitality, and infective agents are close at hand, and the ulcerations should be viewed as secondary results dependent upon location. The spleen and glands are usually not hard or fibrous; the color is often hemorrhagic. It is rare to find large lymphomata in the organs. Narrow strands of lymphocytes lie between the renal tubules, the hepatic lobules, the epithelial columns of the adrenal bodies, the acini of the pancreas, the muscle fibres of the heart; under the sera small collections may be found, and these may be noted in all parts of the body. Infiltration into the nervous tissues has been seldom described, but has occurred in both the central and peripheral systems. Retinitis has been very unusual. The bone-marrow has, in the well-studied cases, always been affected; it has seemed clear in Benda's cases that both hyperplasia of marrow elements and depositions from the circulation occurred there. Benda has noted two points of advance in our knowledge. One is, that the lymphatic "germ-centres" of Fleming are much enlarged, their normal circumscription by resting tissue is lost, and the normal relations of the sinuses and lymph channels are altered; he believes these modifications explain not only the lymphatic hyperplasia, but partly, also, the flooding of the blood stream. The second

point concerns the infiltrations of the vascular tissues. Benda stated that in the lymphatic tissues the walls of the smaller blood channels are often entirely broken through, and that the excessive leucocytes are thus allowed a free passage into blood. Thrombosis does not occur, and to the venous infection be believes the larger part of the excess in the blood is due.

The hemorrhages are constant in the tissues, into the spleen and the viscera, from the mucosa, especially of the alimentary tract, into the serous membranes, and the muscles, including the heart, and not infrequently into the nervous tissues. They are usually small in extent, but may be large, and have produced death when located in the central nervous system. From the mucosa the bleeding has usually been more free. It is rare in any other disease to see hemorrhages into the lymph-glands; they are common here. Hemorrhages occur in the marrow, and could easily be mistaken for splenification. Coagulation in these hemorrhages is the exception, not the rule. Benda believes the infiltration of the walls of the bloodvessels is probably the cause of the hemorrhage.

The parenchymatous alterations are those commonly seen in the febrile infections. Cloudy swelling, hyaline and moderate fatty degeneration comprise the most important changes.

In a number of cases the presence of streptococci has been demonstrated. We are not yet in a position to discuss the possible relation of bacteria to the disease, but we must emphasize its infectious appearance.

Cause. This is unknown. Bacteriological and experimental studies have, unfortunately, so far been without success, except that in a few cases streptococci have been found, which probably were coincidental or instances of terminal infection.

All treatment has been thus far useless. Every case has gone to a lethal ending unmodified by all the varied forms of treatment employed.

The relations between acute leukæmia and acute pseudo-leukæmia will not be here discussed, except to call attention to the very close relation or identity of the two diseases. Every symptom present in acute leukæmia may be present in cases of acute pseudo-leukæmia, save the increase of the white cells. It would seem as though the cases were surely the same, except that for some unknown reason the

leucocytes which are abundant in the diseased tissues are not in the circulation in the cases of so-called pseudo-leukæmia.

Diagnosis. The occurrence of a rapidly occurring anæmia, with its accompanying symptoms, petechiæ over the body, or hemorrhages from the mucous membrane, with enlargement of the lymph glands, fever, and a moderately enlarged spleen and liver, accompanied by a decrease of the red cells and an increase of the white cells of mononuclear form, make the diagnosis conclusive.

The one essential element in the diagnosis is the leukæmic increase of the white cells in the blood of a subject not previously leukæmic.

Hemorrhage may occur in scorbutus, Werlhoff's disease, pernicious anæmia, and purpura; but the increase of the leucocytes, beyond that following hemorrhages, does not occur in these conditions. Indeed, many cases of acute leukæmia are first considered to be one of the so-called hemorrhagic disorders, but the blood count, of course, makes the diagnosis.

Enlargement of the glands and spleen may occur in Hodgkin's disease, tuberculosis, syphilis, and sepsis, but the mononuclear leucocytes are not present in such increased numbers in these diseases, except in rare cases of pseudo-leukæmia. In sepsis and in osteomyelitis the leucocytosis is often extreme, but the white cells are not of the same character, being polymorphonuclear in type. Chloroma and generalized sarcomatosis may, however, approximate the blood-picture. Care, of course, must be taken not to confound the sudden fatal ending of a case of chronic leukæmia with cases of acute leukæmia. It is well known that leukæmia may remain latent for a long while, giving no symptoms except the blood condition. That objection, of course, can hold in many of the cases in this series, but in many of the cases there was no change in the blood in the very beginning, and this developed afterward. Then, too, careful questioning of the patient will usually develop a history of gradually failing health, if leukæmia has really existed before. As most of such cases are of the lymphatic type, the enlarged glands in the great majority of cases would have been discovered before the onset of the acute symptoms.

Prognosis. No case of true acute leukæmia has ever recovered.

Treatment is only symptomatic, care being taken that the patient be made as comfortable as possible until the unavoidable end come.

DISCUSSION.

DR. OSLER: Did I understand Dr. Fussell to say that the limit was sixty or sixty-three days?

DR. FUSSELL: Except in one case—that is, in the cases cited.

DR. OSLER: That seems to me a short limit, for there are cases in which we call it acute leukæmia that exist for three or four months. I have at present under my care a man that has had the glands swollen ever since November, but he has an acute condition with fever, and, rather strange to say, on the first admission to the hospital, in January, his glandular enlargement disappeared completely after inunctions of mercury.

DR. JANEWAY: Out of seven cases of leukæmia which I have had this year one has been acute glandular and one subacute glandular. The first died within two months.

DR. F. C. SHATTUCK: I would like to ask Dr. Fussell whether an autopsy was had in all these cases which he has analyzed?

DR. FUSSELL: No, sir; not in all of them.

DR. SHATTUCK: Do all of them date since the days of differential count?

DR. FUSSELL: No.

DR. SHATTUCK: That error is possible when reliance is placed simply on the number of white cells, as illustrated by the following case: I saw a patient in consultation, some of whose symptoms strongly suggested leukæmia. Making a slide preparation of the blood, I took it to town and sent it to Dr. R. R. Cabot for examination. The doctor telephoned to me very shortly that it was undoubtedly leukæmia, so great was the increase in the number of white cells; but the next day he sent a second message. When he came to stain the preparation he found it to show an enormous leucocytosis. This swung the diagnosis over to that of malignant disease, probably of the left kidney—proved to be correct by autopsy. A more striking illustration of the value of the differential count has not come under my observation.

DR. FUSSELL: We included in the list cases that had the acute hemorrhages, large glands, a spleen enlarging under observation, and an increase in the white cells. Some of these cases were not examined post mortem, but the great majority of them were.

IS A URIC-ACID DIATHESIS AN IMPORTANT FACTOR IN PATHOLOGY?

1. The Physiological Chemistry of Uric Acid.

By VICTOR C. VAUGHAN, M.D.,
of Ann Arbor, Mich.

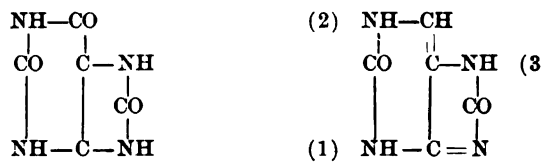
I shall not attempt to discuss with any detail the chemistry of uric acid. This would require more space than I have at my disposal. Moreover, this subject has been elaborately treated in various text-books, and I shall devote my time to the less widely known facts concerning the formation of uric acid in the body and the influence of various physiological and pathological conditions on the same. I am sure that a discussion along this line will be of more practical interest to medical men than a statement of the more purely chemical facts concerning uric acid.

As it is my present duty to open a discussion, I shall not attempt an exhaustive paper, but will endeavor to state my ideas in the form of propositions.

The discovery by Horbaczewski, that uric acid is formed when spleen nuclein is broken up in the presence of certain oxidizing agents, such as fresh blood or dilute solutions of peroxide of hydrogen, has given us the true explanation of the origin of uric acid in the mammalian body, and has served as the basis of numerous researches, some of which have already proved of value to the science of medicine. Before this discovery the chemist had taught us to regard uric acid as a result of imperfect oxidation, the completed product of which is urea, but the physiologist had been unable to satisfactorily demonstrate this supposed relationship between urea and uric acid. The experiments of Horbaczewski show that the amount of uric acid and other xanthin substances formed in the body is a measure of nuclein metabolism. In other words, it indicates the relative number of nucleated cells that

are at the time undergoing disintegration processes. The researches of Hoppe-Seyler, Miescher, Kossel, and others, on the nucleins opened up the way for the discovery of Horbaczewski, and have since confirmed and amplified the value of his research.

Uric acid belongs chemically and physiologically to a group of substances sometimes known as nuclein bodies, because they have their origin in cell nuclei. In this group, besides uric acid, we find adenin and hypoxanthin or sarkin (known as the sarkin bodies), guanin, xanthin, heteroxanthin, paraxanthin, theobromin, theophyllin, caffein, and carnin. All of these, with the exception of uric acid, are basic in character, and are generally designated as xanthin bases. Kossel and Krüger have proposed that these bases, together with uric acid, might be designated as alloxuric bodies, because all of them contain both alloxan and urea residues. The constitution of uric acid and xanthin is shown by the following graphic formulæ, determined by Fischer:



Uric acid. Xanthin.

It will be seen that xanthin contains three imido groups, and by the replacement of a hydrogen atom of either of these with a methyl group a monomethyl xanthin results. Three monomethyl xanthins are possible according to the imido group replaced. Krüger and Solomon have shown that heteroxanthin is a monomethyl xanthin with a methyl group substituted for the hydrogen of the imido group in position (3). By the substitution of two methyl groups three compounds are possible. Theobromin is formed in this way by substitutions in the imido groups (2) and (3), and theophyllin by substitutions in groups (1) and (2). Paraxanthin is probably the third dimethyl xanthin, but this has not been positively demonstrated. Caffein is trimethyl xanthin. Theophyllin and caffein are not known to be constituents of the animal body, but the fact that they are constituents of beverages quite universally employed by man renders their close chemical relationship to other members of this group a matter of physiological interest.

I have stated that the amount of the alloxuric bodies formed within the organism is a measure of the extent to which nuclear disintegration is going on. It will, therefore, be desirable for us to inquire into the chemical constituents of cell nuclei, because we must then find the antecedents of the alloxuric bodies. It is probably true that no two kinds of cells have nuclei of exactly the same composition. Differences in function indicate variations in chemical composition and structure, and so far as cellular chemistry has advanced this indication has been confirmed. It will be best to review briefly the facts that have been so far ascertained concerning the chemical composition of cell nuclei.

The lymphocytes of the thymus gland have large nuclei, which constitute the greater part of the cell, and for this reason, as well as from the fact that they can be obtained in abundance and quite free from other tissue, these corpuscles furnish suitable material for the study of the chemical composition of the cell nucleus. Lilienfield has made a most valuable contribution to our knowledge of the composition of nuclear substance in his researches on these lymphocytes. He has found that these corpuscles in the dry state yield more than 68 per cent. of a body, to which he has given the name nucleohiston, and less than 2 per cent. of albumin. These figures probably fairly represent the relative amounts of nuclear substance and cytoplasm in these cells. It may be remarked that Lilienfield has found nucleohiston not only in the lymphocytes of the thymus and lymphatic glands, but also in the cells of the spleen, in the testicles, the unripe spermatozoa of the carp, and in the epithelial cells of the small intestines. This nucleohiston is probably identical with the "tissue fibrinogen" with which Wooldridge, some years ago, secured immunity against experimental anthrax. Wooldridge believed that this substance was a compound of lecithin and an albumin.

Nucleohiston may be extracted from finely divided thymus glands with water, and precipitated from the aqueous solution with acetic acid, avoiding an excess in which the recently precipitated body is soluble. The moist substance is soluble in dilute acids and alkalies and in dilute neutral salt solution. It is worthy of note that nucleohiston gives the Millon and xanthoproteic reactions, and the biuret coloration faintly on standing. It contains a little more than 3 per cent. of phosphorus. Novy found that subcutaneous injections of 0.3 gram or more in rabbits cause an elevation of temperature of from 1°

to 1.5° C., preceded by a short period of subnormal temperature. Nucleohiston, as well as its nucleinic acid constituent, precipitates diphtheria toxin; but, as Novy states, this undoubtedly is a mechanical effect; the toxin being carried down with the precipitated proteids. However, nucleohiston does have some destructive action on diphtheria toxin after the mixture has stood for some time in vitro, although separate injections do not protect animals (Novy).

Nucleohiston is easily broken up into histon and nuclein. This can be accomplished by artificial gastric digestion or by the action of 0.8 per cent. hydrochloric acid on an aqueous solution, or by boiling the aqueous solution. The nucleins obtained from nucleohiston by these different methods are very similar, but apparently not identical.

Histon was discovered by Kossel, in 1884, in the nuclein of the red corpuscles of the goose. It has marked basic properties, but in other respects it resembles the peptons. It gives the biuret reaction. Histon is precipitated from its aqueous solution by saturation with neutral salts; thus a relationship to the globulins is indicated. Its basic character is shown by the fact that it is thrown down from aqueous solution of its hydrochloride on the addition of ammonia. When injected intravenously histon destroys the coagulability of the blood, but histon plasma is quite unlike so-called pepton plasma. The views of Lilienfield on the influence of nucleohiston and its components in coagulation will be stated later. Novy has shown that histon is much more poisonous than Lilienfield believed. Two hundred milligrams often killed guinea-pigs weighing 300 grams or less. Repeated injections not only failed to establish tolerance, but apparently increased susceptibility. Necrotic areas often formed about the point of inoculation in animals that recovered. The effect on the temperature is similar to that of nucleohiston.

From the results obtained by Wooldridge and some subsequent investigators, it has been suggested that histon might have antitoxic properties. The careful researches of Novy on this point fail to confirm this belief. He finds that histon does not protect against separate subcutaneous injections of the toxins of diphtheria and tetanus, or against inoculations of the bacilli of anthrax and hog cholera; that in a mixture of histon and diphtheria toxin, the latter is destroyed in a few minutes, but that this is due in part, if not wholly, to the acidity of the histon solution.

The leuconuclein, the body conjugated with histon in nucleohiston, is easily decomposed into an albuminous substance and nucleinic acid. With the former we are not concerned, but nucleinic acid is, for the purpose of the present inquiry, the most important constituent of the nucleus. Nucleinic acid is characterized by (1) its large phosphorus content, nearly 10 per cent.; (2) the fact that on being broken up it yields xanthin bases; and (3) by its marked germicidal properties. All nucleinic acids, so far as studied, those from yeast-cells, spleen, marrow, spermatozoa, nervous tissue, the thymus, etc., are bactericides. This property of the nucleins, discovered by the writer in 1893, has been confirmed by Kossel and others. To furnish the germicidal nucleinic acid is apparently one of the most important functions of the leucocytes, and in setting free this substance the corpuscle itself most probably is destroyed.

Although it has no direct bearing on the physiology of uric acid, it may be of interest to insert at this place Lilienfield's views concerning the influence that nucleohiston and its components have upon the coagulation of the blood. He says: "The leucocytes contain in their nuclei a markedly acid substance, nucleohiston, which, when added to spontaneously coagulable fluids, or to cold filtered horse-plasma, or to proplastic and fibrinogen fluids treated with fibrin ferment, retard their coagulation greatly. Caustic lime and caustic baryta split up nucleohiston into leuconuclein and histon. Nucleohiston dissolved in lime or baryta water causes coagulation in proplastic and fibrinogen fluids. From the above the following conclusions may be drawn: (1) Histon is the coagulation-retarding constituent of nucleohiston; (2) leuconuclein is the coagulation-hastening constituent. Naturally after having the histon split off, nucleohiston loses its retarding action on coagulation. Leuconuclein and nucleinic acid are not in and of themselves capable of producing fibrin from fibrinogen. They split off from fibrinogen thrombosin, the immediate antecedent of fibrin, and then, on the addition of a soluble lime salt, thrombosin is converted into fibrin. By employing a solution of nuclein in lime-water both steps in the process are accomplished. The nuclein splits off the thrombosin which in the lime solution passes into fibrin. . . . The intensity of this effect is in direct proportion to the amount of nucleinic acid in the nucleoproteid molecule and is greatest when nucleinic acid itself is used. . . . Fibrin is a lime compound of thrombosin."

Lilienfield found that neutral solutions of nucleohiston injected into the jugular vein of living animals caused the formation of thrombi, while the blood allowed to flow from the carotid remained fluid. Injection of neutral solutions of histon hydrochloride to the extent of 0.3 g. to each kilo. of body-weight renders the blood subsequently drawn non-coagulable. Injections of neutral leukonuclein solution cause the formation of thrombi, and the blood subsequently drawn coagulates instantaneously.

It must not be inferred that all nucleinic acids cause coagulation of the blood: the writer has injected large quantities of yeast nucleinic acid intravenously in rabbits and as much as 1 gram of this acid in man without causing any such effect. Moreover, the statements of Lilienfield, as quoted above, have been very properly criticised by Hammarsten and Cramer, who believe that Lilienfield's so-called thrombosin is nothing more than slightly altered fibrinogen.

It is possible that the slowness with which blood sometimes was seen to coagulate in the old days of venesection, giving time for the partial subsidence of the red corpuscles and the formation of the "buffy coat" of leucocytes, was due to the presence of an unusual quantity of histon in solution, and that our professional ancestors were not far out of the way when they attributed this phenomenon to an inflammatory condition of the blood.

Nucleinic acid on being decomposed yields the nuclein bases and thymic acid. The kind and amount of nuclein bases yielded by different nucleinic acids are by no means constant. Yeast nucleinic acid, on being heated with dilute mineral acid, yields relatively large quantities of adenin, hypoxanthin, guanin, and xanthin. In his earlier work on thymus nucleinic acid, Kossel was able to detect among its decomposition products only one of the nuclein bases, adenin, and he proposed that this nucleinic acid should be called adenylic acid. More recently, however, he has found in addition to adenin not only guanin, but a new base, cytosin. It will be best, for the present at least, to designate the different nucleinic acids by the source from which they are obtained, and we shall continue to speak of yeast nucleinic acid, thymus nucleinic acid, etc. Of thymic acid it is necessary to say only that it contains all the phosphorus present in the original nucleohiston molecule, and that it can be decomposed into a base, thymin, and lævulinic and phosphoric acids. The fol-

lowing represents the steps in the breaking up of the molecule of nucleohiston:

- Nucleohiston
  - Histon
  - Nuclein
    - Albumin
    - Nucleinic acid
      - Nuclein bases
      - Thymic acid
        - Thymin
        - Lævulinic acid
        - Phosphoric acid

I have gone somewhat into detail concerning the composition of the nucleus of the leucocyte, because, when we come to study the phenomenon of chromatolysis, in which process uric acid is formed, we must know something of the antecedents and the by-products before we can estimate the cost or appreciate the real value of the special product. Indeed, I must say a few more words concerning the chemical composition of nuclear substance. In many cells the basic histon is not present, and in its place there is found a basic proteid of much simpler molecular structure. These proteid bases are known under the general name of protamins. Miescher, who may be regarded as the discoverer of nuclein, in 1874 obtained a basic substance to which he gave the name protamin, from the spermatozoa of salmon. This base is combined in these cells with nuclein. In 1894 Kossel took up the study of protamin, and he has since shown that in the spermatozoa of many animals there are proteid bases combined with nuclein. In no two animals are the basic substances identical, and Kossel proposes that the name protamin be used generically, and he calls the base obtained from the spermatozoa of the salmon, salmin, and that from the sturgeon, sturin. Kossel is of the opinion that a protamin group will be found in all proteids, and that it is from this group in the proteid molecule that leucin and basic substances are derived. He is also inclined to the opinion that the histon of nucleohiston consists of a protamin combined with an albumose. In fact, he has prepared such a compound, which he states gives all the reactions of histon. However, before it can be definitely shown that the protamin group is contained in histon it must be shown that protamin derivatives can be obtained from histon. On being heated with sulphuric acid and water a protamin can be split up into histidin and arginin. The last-mentioned base was discovered by Schulze in the conglutin of lupin sprouts, and later was obtained by Hedin in the decomposition of

horny substance with hydrochloric acid and stannous chloride. Schulze and Likiernik have shown that arginin, on being heated with baryta, yields urea. The protamin molecule contains the basic group, but does not contain the tyrosin or amido-acid group. This encourages us to hope that the structure of the proteid molecule will sometime be known.

Recently, H. Kossel has demonstrated the very interesting and important fact that the protamin sturin has marked bactericidal properties. This shows that the nucleated cell has, in addition to its nucleinic acid, a germicidal basic substance. This is additional evidence that certain animal cells are well protected against bacterial invasion.

Mathews, working under Kossel, has recently studied the spermatozoa of the boar, bull, herring, and the sea-urchin Arbacia. He finds that the sexual cells of the herring consist principally of nucleinic acid combined with a protamin to which he gives the special name clupein, that the basic substance in the spermatozoa of the sea-urchin is more nearly related to histon than to protamin, and that those of the bull and boar contain neither protamin nor histon.

We are now ready to proceed to the study of the origin of the alloxuric bodies in the body. It will be evident from what has already been given concerning the chemistry of nuclear substances that the alloxuric bodies can originate only when there is nuclear disintegration, and then not until the nucleinic acid is broken up. The dissociation of the basic substance and the nuclein is not enough to lead to the formation of the alloxuric bodies. Indeed, nucleinic acid may be set free and manifest its germicidal action without the production of uric acid and its immediate antecedents. The destruction of the nuclear substance must be quite complete before these bodies are formed. The solution and disintegration of nuclei is designated as the process of chromatolysis. Some of the conditions under which the alloxuric substances may be formed in the body may now be stated.

1. Every nucleus comes from a parent nucleus. Every cell must at some period of its existence be nucleated. No cell can be built up or organized except through the agency, direct or indirect, of a nucleus. Every cell which is capable of reproduction must contain a nucleus. I do not mean to say that a certain amount of cyptoplasm is not also necessary to reproduction. There may be some differences

of opinion on this point, or the nuclei of some cells may require cytoplasm, while the nuclei of other cells may not, but there can be no doubt that the existence of a nucleus is essential to the process of reproduction. However, this is not the sole function of the nucleus. As has already been stated, the nucleus is essential to organization. Cells that are never to reproduce themselves are organized through the agency of nuclei. Biologically, the nucleus is that part of the cell which is essential to growth and reproduction. Quantitatively, it may constitute the greater part of the cell, or it may be relatively a very minute fraction of it. Developmentally, it is that part of the cell that determines both form and function. From the stand-point of heredity, the nucleus is that part of the cell through which generic and specific form and function are transmitted. It is that part of the cell that makes life potentially, at least, continuous. Nuclein is the material of which nuclei are composed. Many of the cells formed in the animal body are destined, after having reached a certain period of growth, solely to serve other cells. These may, and some of them certainly do, lose their nuclei after having reached the stage of development necessary for them to reach before they can perform the function for which they are brought into existence. Chromatolysis and cell disintegration are not in these cells simultaneous processes. The erythrocytes of mammals are cells of this kind. Erythroblasts may be studied in the spleen and bone-marrow of both young and adult animals. The formation of erythroblasts in the spleen of the adult animal in a normal condition is slight, and some deny that it occurs. I am not going into a description of the well-known changes observed in the formation of these cells. I wish only to call your attention to the fact that the nuclei after having perfected the red blood-corpuscle, so that it may serve as a carrier of oxygen, disappears, and, so far as we know, is not further utilized. The suggestion that the nuclear substance of the erythroblasts, after having performed its function in the organization of the cell, may be utilized in the building up of some proteid of the plasma, does not affect the general statement here made, even if it be true. It matters not for the present purpose whether the chromatolysis observed in these bodies is accomplished by a gradual solution of the nuclein or a more active expulsion of the nucleus, the result is the same in either case. Nuclein is broken up, alloxuric bodies are formed, and uric acid, the most highly

oxidized of these substances, is the chief representative in the urine of the nuclear metabolism resulting, as here indicated, in the body. As the formation of red blood-corpuscles is a continuous process, this source of the alloxuric bodies is a never-failing one. The modifications to which it is subject in disease need not be discussed here. During fœtal and early extra-uterine life, the number of the cells undergoing this kind of chromatolysis must be relatively much greater than subsequently. It must not be inferred that chromatolysis without simultaneous cell disintegration is confined to the red corpuscles. I have referred to these as a suitable illustration of a process that goes on to a greater or less extent in other tissues.

2. The leucocytes are a constant but quantitatively variable source of the uric acid and other alloxuric bodies. The biology of the leucocyte is now one of the most interesting problems in medicine. Within a few years past it has been demonstrated that an increase in the number of leucocytes in the blood is followed by increased elimination of alloxuric bodies. However, there are exceptions to this rule. It is too early yet to attempt a scientific classification of the different forms of hyper- and hypo-leucocytosis. However, this need not deter us from gathering together the somewhat meagre and incomplete facts we have on the subject, and endeavoring to read the lessons they teach us.

There may be hyperleucocytosis without consequent increase in the amount of alloxuric bodies eliminated. The researches of Küknau have demonstrated this. It has long been known that the intravenous injection of inert substances, such as cinnabar or carbon in finely divided form, will cause a great increase in the number of leucocytes in the blood. After a short time no free particles of the dust can be found in the blood, but the leucocytes are laden with the particles. Hoffmann and Lungerhaus observed these pigment-bearing corpuscles twenty days, and Ponfick seventy days, after the injection of the dust. They are found most abundantly in the small capillaries, where the leucocytes undoubtedly have the best opportunity, on account of the slow movement of the foreign particles, to absorb them. Then the leucocytes bear the foreign particles out of the bloodvessel, and, apparently at least, permanently deposit themselves with their burden in some extra-vascular cell. I say apparently, because we cannot positively assert that the corpuscles remain permanently with the par-

ticle. However this may be, the studies of Küknau have shown that there is no increased elimination of alloxuric bodies following the most marked hyperleucocytosis induced in this manner. These experiments are of further interest, inasmuch as they indicate that the life of the leucocyte may be much longer than is usually supposed to be possible.

In the second place, there may be hyperleucocytosis, with increased elimination of the other alloxuric bodies, but with no increase, and sometimes with a marked decrease in the amount of uric acid formed and eliminated. This seems to be true in the graver anæmias. However, more extended investigation along this line is desirable. Küknau suggests that this may be ascribed to deficient oxidation due to the great decrease in the red corpuscles, since Horbaczewski has shown that nuclein must be broken up in the presence of an oxidizing agent in order to yield uric acid. It should be stated that it is not supposed that the xanthin bases are formed and then oxidized into uric acid. When nuclein is oxidized and then broken up it yields uric acid and the xanthin bases. When broken up without previous oxidation, it yields the xanthin bases, but no uric acid. Kolisch and Stejskal report a case of anæmia gravissima terminating in death within a few days, in which the uric acid was much below, and that of the xanthin bases greatly above the normal. The studies of Neusser and of Westphal, in which the former reported an excess and the latter a deficiency of uric acid in pernicious anæmia, do not throw any additional light on this subject, inasmuch as they failed to estimate the other alloxuric bodies. The experimental studies in which the red corpuscles have been destroyed by the use of some dissolving agent show somewhat diverse results. However, it is, so far as I know, quite generally true, that marked destruction of the red corpuscles is accompanied or followed by hyperleucocytosis, the increase in the leucocytes being absolute as well as relative. I believe this to be true in malaria, although the evidence on this point has been somewhat conflicting. The difference in the observations is apparently due to the time with reference to the paroxysm when the leucocytes have been counted. Küknau probably states the facts correctly when he says that during the paroxysm blood pigment is set free. The large polymorphonuclear leucocytes in the spleen and marrow absorb the red corpuscle detritus, infected red corpuscles, and entire plas-

modia. During this stage the leucocytes will be found in diminished number in the blood. After the paroxysm the melaniferous leucocytes appear in the blood. This is the stage of hyperleucocytosis. It is of short duration and is followed by leucolysis and a consequent increase in elimination of both uric acid and the other alloxuric bodies. The same investigator found a similar decrease in the red corpuscles with subsequent hyperleucocytosis and augmented climination of alloxuric bodies after subcutaneous injections of pyrogallol. A priori, it might be inferred that the hæmoglobin from the broken-down red corpuscles is the leucotactic substance, but Küknau found that intraperitoneal injections of hæmoglobin have but slight leucotactic or leucogogic effect.

In the majority of instances of hyperleucocytosis there is subsequent leucolysis and a consequent augmentation in the amount of alloxuric bodies, including uric acid. This is true of digestion leucocytosis and of that which follows the injection of nuclein. It is also true of the leucocytoses that accompany various inflammatory diseases.

It would be of great interest to us could we know the successive products that result from the disintegration of the leucocytes. Much more extended and exact research is necessary before we can speak very definitely on this point. However, the idea that the value of a hyperleucocytosis in combating an infectious disease is to be measured by the number of leucocytes without reference to the agent used to increase their number is certainly wrong. That a hyperleucocytosis induced by nuclein and allied bodies does augment the germicidal properties of the blood and increase the resistance of the animal body against certain pathogenic micro-organisms, has been demonstrated by the researches of Wooldridge, the writer, Grammatschikoff, Pawlowski, Loewy and Richter, Hahn, Jacob, and others. These have uniformly found that a nuclein hyperleucocytosis does slightly increase the resistance of the body against the bacterial infection. All, furthermore, conclude that the extent to which the resistance can be increased by this means is, with present means, limited. That every hyperleucocytosis does not increase the resistance to infection has been shown by direct experiment. It is well known, for instance, that the injection of pilocarpin causes an extraordinary hyperleucocytosis, and yet an amount of a culture of the pneumonococcus, from

which the control might escape, and the nuclein animal would surely not be affected, kills the pilocarpin animal, notwithstanding the great increase in leucocytes. Whether this is due to the depressing action of pilocarpin on the heart, as supposed by Loewy and Richter, or to some other cause, cannot be at present stated. It is certainly true, that in some forms of leucolysis nucleinic acid is set free, and to this must be ascribed the increased germicidal action of the serum obtained from hyperleucocytotic blood. It has been found to be necessary to modify the phagocytic theory of Metschnikoff. It is now generally agreed that the leucocyte combats the bacillus by virtue of some chemical constituent of the former.

The question now is whether we are to believe, with Buchner, that his so-called alexins are secretions of the leucocytes, or that the leucocyte disintegrates, and that one or more of the substances resulting from this disintegration acts as a germicidal agent. Havet seems to have been the first to show that in hypoleucocytosis the germicidal action of the blood is reduced, while, on the other hand, in hyperleucocytosis the bacterial action is augmented. Hahn has confirmed the second half of this statement.

The following reasons may be given for the belief that the increase in the germicidal properties of the blood following hyperleucocytosis is due to leucolysis, and is not a result of an increased secretion of a germicidal substance by the leucocytes:

(*a*) By artificially breaking up the leucocytes outside the body a germicidal substance, nucleinic acid, is obtained.

(*b*) Increased elimination of the alloxuric bodies follows hyperleucocytosis, in all instances, with the exception already stated.

(*c*) The microscopical studies of Botkin and Löwit show that hyperleucocytosis is followed by an increased quantity of leucocytic débris in the blood.

(*d*) The experiments of Loewy and Richter show that hyperleucocytosis is followed by the appearance in the blood of albumoses, which are not found under normal conditions or are found only in minute traces. These albumoses are believed to come from the disintegration of the leucocytes. However, I must state that I do not consider the method employed by these investigators wholly free from chances of error.

Experiments made to determine whether or not change in leuco-

cytotic content alters the glycolytic property of the blood, have been contradictory, and, consequently, do not furnish evidence for either side of this question.

Whether the hypoleucocytosis that immediately follows the injection of nuclein, albumose, bacteria, toxins, etc., is due to leucolysis or to leucopenia, has not been positively determined.

3. A third source of uric acid and allied bodies is in the food. It has long been known that increased consumption of animal food increases the amount of uric acid formed in the body. This increase is probably due to two causes: (1) Meat contains nucleo-proteids and alloxuric bodies in small amount. (2) Digestion leucocytosis is greatest after meals rich in animal food, and is likewise increased by alcoholic beverages. The fact that nuclein-containing foods increase the amount of alloxuric bodies formed and eliminated has been demonstrated by several investigators, among whom we may mention Umber, Mayer, and Hess and Schmoll. It is needless to dilate upon these statements.

4. The physiological disintegration of various nucleated cells in the body must contribute slightly to the formation of alloxuric bodies. This is especially true of epithelial and glandular cells. According to the studies of Weintraub, 100 grams of meconium contain from 0.3 to 1.0 gram of uric acid, and the daily stool of an adult from 0.1 to 0.5 gram of alloxuric bases.

5. Some poisons, such as lead and alcohol, stimulate certain cells to abnormal proliferation. Karyokinesis takes on a pathological significance, and many of the rapidly forming cells break down and their nuclei suffer dissociation changes.

6. Certain pathological growths are accompanied by marked cell proliferation, and as many of these cells, including their nuclei, disintegrate, this may be a source of uric acid and allied bodies in cases of carcinoma, etc. However, the scope of the work assigned me by your committee does not require me to go into a discussion of pathological conditions, and I gladly leave their consideration to those who can speak more authoritatively.

2. The Uric-acid Diathesis from a Clinical Stand-point.

By WILLIAM H. DRAPER, M.D.,
of New York.

Recent physiological experiments tending to elucidate the long-vexed question in the chemistry of nutrition as to the origin of uric acid have renewed discussion as to the relation of an accumulation of uric acid in the blood and its output in the urine to many morbid conditions of which it has been assumed to be the determining cause. Gout may be strictly said to be the only disease which has thus far been shown to be directly and invariably associated with the accumulation of the salts of uric acid in the blood-serum; as to those many and varied derangements of function and structure which are so generally ascribed to the blood state defined as lithæmia, it must be admitted that the evidence lacks the definite and exact value which we have in the case of the generic disease. Indeed, it must be said that the correlation of so-called lithæmic diseases with gout rests mainly upon deductions from clinical evidence, and must yet be confirmed by more exact physiological research.

The list of the morbid states in which we may suspect, for chemical reasons, an increase of formation of uric acid from its increased elimination, based mainly upon an increased proportion of uric acid to the urea in the urine, include a vast variety in morbid conditions, some showing that it is often only a transient increase, some a more or less persistent one.

Those of us who have for years clung to the old suboxidation theory, which made the complex chemistry of the body so simple when we considered the final destiny of a nitrogenous molecule to be urea, and of one of the carbohydrates to be carbonic acid and water, are compelled to admit that the more the chemistry of the vital processes of nutrition is investigated, the more complex the problem becomes. We certainly are no longer justified in believing that uric acid is necessarily the penultimate of urea because we can convert it into

urea by oxidation in the laboratory, since recent investigations tend to show that it is derived from a special albuminous element, the nuclein in the nuclei of the white blood-cells, and it is asserted that uric acid with its allied leucomains—xanthin and hypoxanthin, guanin and adenin—can be obtained from the destructive transformation of nuclein. The often observed, persistent elimination of uric acid in cases of anæmia and splenic leukæmia has been asserted to be a clinical confirmation of the relation of leucocytosis to uric-acid excretion. Horbaczewski has also found, by actual experiment, that feeding rabbits and starving men on spleen pulp will increase largely the excretion of uric acid, and that drugs which increase leucocytosis are followed by an increase of uric acid; and, contrariwise, that drugs which diminish leucocytosis will diminish uric acid.

While it may be justly questioned, however, whether these experiments are as yet conclusive as showing the origin of uric acid in the process of retrograde tissue metabolism and in a special class of proteid foods, they are interesting as suggesting a possible variation in the transformation of nutritive elements according to their original constitution. Here, again, all that we can say at present is that the complexity of the problem of nutrition increases the more we explore it. It has been truly observed that, though we may be led to accept the evidence of Horbaczewski as to the nuclein origin of uric acid as a working hypothesis, we must acquire more evidence than we now have to prove that it is the principal source of uric acid. Especially is this needed to explain the large excretion of uric acid in birds and snakes, where it takes the place of urea, and where, as yet, we have only the teleological explanation that it is destined for a solid rather than a soluble excrement. It has always appeared to be a curious biological fact that in animals in which the conditions for rapid oxidation were so opposite in activity as they are in birds and snakes the nitrogenous waste should be of the same nature. It would seem to be necessary to show, according to Horbaczewski's views, that the diet of birds and snakes should be composed of substances rich in nuclein or some other substance which may be proved to undergo in the body a similar transformation.

The chief interest, however, to the clinician, of these considerations as to the origin of uric acid lies in their bearing upon the elucidation of the widely accepted views, at present, as to their etiological relation

to the subjective symptoms and objective lesions which are so generally ascribed in these days to lithæmia, uricacidæmia, or to what is called more commonly, perhaps, the lithic-acid diathesis, to gout and the gouty habit. As we have said, excepting as regards the arthritic inflammation known as gout, there is no one of these terms which is justified by the crucial test of relating the disease directly to a demonstrable cause, or rather to an invariable incident in its history. Since the demonstration of Garrod, fifty years ago, of the salts of uric acid in the blood-serum of sufferers from gouty arthritis, there has been no question as to the fact, though there has been infinite discussion of its true relation to the nature and determining cause of the process by which the paroxysms were produced. Two well-ascertained facts embarrass us: first, we know that uric acid may accumulate in the blood, temporarily, at least, and not produce gout; secondly, we know that gout may occur without any positive evidence in the blood-serum that there is an excess of uric acid, or in the urine that there is an undue elimination of it. I think the testimony of all experienced observers of arthritic gout will confirm these propositions. These facts and others which might be mentioned have driven the advocates of the uric-acid theory to invoke the aid of the nervous system to supplement its defects and explain otherwise the pathological process. As a result, we have now what has been called the neuro-chemical theory, a theory which, perhaps better than any other, correlates the diseases which pass under the name of gout and rheumatism, especially those mixed varieties recognized as gouty rheumatism, rheumatic gout, chronic and subacute rheumatism.

It, of course, cannot be assumed that the relationship of gout and rheumatism is reasonably based upon the recognition of the existence of lithate of soda or of any other common *materies morbi*, but I would take the liberty of calling your attention to certain anatomical facts and clinical features upon which we may, I think, correlate diseases which have hitherto too generally, perhaps, been regarded as distinct pathological entities. The differential diagnosis of the diseases just mentioned has always been, and still is, a puzzling problem to pathologists and practitioners, and it may be said that there is nothing absolutely common to them all except what we may call arthritism, which recognizes a common seat in the structural anatomy of the joints, their contiguous fasciæ and tendinous appendages, or,

in a word, in the connective tissues wherever found—whether in the bloodvessels, nerves, or integumentary and glandular structures. This common anatomical site is certainly an important feature in gout and rheumatism in all its polymorphic manifestations, however we may differ as to the determining cause of the lesions. In regard to gout we have a pretty general consensus as to the recognition of uric-acid blood state as a coincident but not invariable element. In regard to acute inflammatory rheumatism, or rheumatic fever, in which we have discovered no special blood dyscrasia, since we have discarded, as unproved, the lactic-acid theory, authorities are now inclined to reckon it among the specific infectious fevers, perhaps bacterial in its origin, so that, between these two apparently most distinct forms of articular inflammation, excepting for clinical reasons which will be hereinafter mentioned, we must conclude that the only common basic relation is the anatomical one, and that the only reason to suppose that these diseases are in any way related lies in the fact that in those who are exposed to these affections, for some cause, inherent in the individual, hereditary or acquired, these structures are especially vulnerable. Why they are so vulnerable, and whether the diseases which affect them are defined as to their cause, or related to each other etiologically through a single pathological cause, or through a combination of allied causes, are problems which await solution.

In an endeavor to correlate gout and rheumatism in their varied forms, we can only rely, therefore, upon clinical evidence and a reasonable consideration of such evidence based upon the trustworthiness of those who have had large opportunities of studying these diseases in their family and personal anamnesia.

The experience of clinical observers in what, I think, we might call for convenience arthritism, tends toward the acceptance of the view that gout and rheumatism are in some way allied, in spite of the inconstancy of a demonstrated materies morbi common to them both. A common anatomical seat shows nothing, of course, but a special vulnerability in the victims as to their joint structures, and, we hope to show, as to their connective tissue wherever it enters largely into the organs which are sometimes involved in the disorders to which gouty and rheumatic persons are liable.

In support of this assertion I would first instance the mixed forms of gout and rheumatism in the same individual, in different individ-

uals in the same family, in the greater liability of the men to true gout and of the women to rheumatism, in the common occurrence of gout and rheumatism in the children of gouty parents, for which there seems to be no other explanation than a special vulnerability of the joint structures, along with an extreme susceptibility to atmospheric changes, to certain common derangements and reactions to certain kinds of food in digestion, and, perhaps, to the invasion of particular pathogenic infections. I think the experience of most clinical observers will accord in the general truth of these assertions. While we may agree in the proposition that true podagra, for example, is an unmistakable sign of uric acid in the affected joints, it cannot be assumed that it is the sole conclusive indication of gouty disease. A distinct vulnerability of the tissues which enter largely into the joint structures, as shown by more or less frequent repetition of inflammatory attacks following excesses, and sometimes extremely moderate indulgence in the ingestion, for example, of fermented wines, beers, sweet fruits, and an excess of carbohydrate foods generally, rather than, as has commonly been supposed, of nitrogenous foods, constitutes, in the experience of many observers, a truly gouty state, though the evidence of uric-acid accumulation in the blood-serum or an excessive output in the urine may be absent. This inconstancy in the presence of uric acid as an objective sign of gout, or what is recognized as a gouty vice of the body, appears to give justification to the idea which has been suggested that uric acid is, perhaps, after all, not the only or the special offending substance in gout, but rather its chief objective incident, one of the epiphenomena, so to speak, in the retrograde metabolism of the food and tissues.

Next to the analogies existing in the symptoms and structural changes of all forms of arthritic disease, the most striking feature of them is their tendency to perpetuate themselves by inheritance or to be created *de novo* by special habits of eating and drinking. I have already alluded to this feature in the history of the forms in which uric-acid deposits constitute the most striking objective sign, but it is true also in my experience in those subacute and chronic forms ordinarily called subacute, chronic or gouty rheumatism resulting in crippling of the joints.

These are not, in the classical sense of showing deposits of urates in the joints, gouty diseases, but my clinical experience leads me to

believe that in many of them a gouty ancestry may be traced which has determined a vulnerability of the joint tissues, sometimes with, but often without, the accompanying signs of derangements of nutrition common to the victims of gouty disease.

Rheumatoid arthritis, arthritis deformans, what is called senile rheumatism, which is part of the sclerotic degeneration of old age, is a form of disease which recognizes a distinct cause, probably a peripheral nerve lesion, and has perhaps only a remote, if any, alliance to gout.

As to the so-called gonorrhœal rheumatism, while I am not disposed to altogether ignore its dependence upon specific blood infection, I believe that it, like gleet, is especially liable to complicate gonorrhœa in persons who have a gouty heredity. I had this disease in mind when I spoke of the possible susceptibility of gouty persons to the invasion of certain pathogenic infections. My own clinical experience has repeatedly suggested this association, and several observers, notably Dr. Ord, of London, have affirmed that in similar catarrhal affections of the female generative organs a gouty heredity is often present, and probably accounts for their well-known rebelliousness to treatment. The alliance of gout, therefore, to many forms of rheumatism, while it has not been established in them through the presence of uric acid either in the blood-serum or of deposits of urates in the joints, is, I think, suggested through the common vulnerability in gout and rheumatism of the joint tissues to inflammatory processes.

The likeness as to tissues and structures involved and their vulnerability constitute in themselves, to be sure, a slender foundation upon which to establish a common pathology for gout and rheumatism, though they are suggestive considerations. As we have said, however, there are certainly mixed forms of gout and rheumatism in which the diseases appear to be combined in both local and constitutional features, and are apparently correlated through inheritance and family peculiarities. In addition, therefore, to the vulnerability of similar structures in the two diseases, there is the perpetuation of this vulnerability by inheritance, and also the fact—which, I think, clinical experience justifies us in speaking of as a fact—that cases of gout and rheumatism are found in different individuals of the same family, the men more often being liable to gout and the women to rheumatism. We have, too, distinctly mixed forms, sometimes described as rheu-

matic gout, on account of the presence in both of certain constitutional peculiarities, some of these, such as disturbances of digestion and special reactions to particular foods and drinks, being characteristic of gout, and a great sensitiveness to the evil effects of refrigeration of the surface, either local or general, being strikingly characteristic of rheumatism. In my experience these characteristic features of the two diseases may be present in the same individual.

Mr. Jonathan Hutchinson, in an able address in the discussion on the "Relations which Exist between Gout and Rheumatism," at the International Medical Congress in London, in 1881, defines gout as a tendency to arthritis from blood disorder, and rheumatism as a tendency to arthritis in connection with catarrhal nerve disturbances, and, in his opinion, based upon a large experience, there is nothing antagonistic in these two classes of causal influence; the person who gets his blood disordered when he drinks strong wine or beer being, as we believe clinical evidence shows, especially liable to catch cold in his joints when exposed to cold and dampness. If this proposition is admitted on clinical experience, much of the difficulty in the differential diagnosis of gout and rheumatism disappears, and the correlation of these diseases is made probable, not through the common presence in both of a single *materies morbi*, but through a common nervous sensibility as a large determining factor in arthritism.

In this connection it is interesting and important to mention that the association of catarrhal diseases with true uric-acid arthritis is a well-recognized clinical fact. Catarrhal and parenchymatous tonsillitis and pharyngitis, tracheitis, bronchitis, acute and chronic, with or without spasmodic asthma, gastro-enteric catarrhs, genito-urinary catarrhs, catarrhs with or without lithiasis, are common in the clinical experience of every practitioner who is familiar with the history of gout in its varied manifestations. In this connection we might also refer to the frequency of recurrent attacks of iritis and other forms of ophthalmic inflammation in connection with gout.

The same statement may be made of catarrhal affections of the cutaneous integument, as has been abundantly proved by the experience and writings of Garrod, Duhring, and other observers who have followed in the lead of the French dermatologist, Bazin, who have had their attention especially drawn to this frequent liability of

distinctly gouty and rheumatic subjects to eczema in its various forms, including the varieties of keratosis or the scaly and seborrhœic affections of the skin. My own experience in this class of diseases leads me to believe that gout and rheumatism are often recognized in the personal or family history of sufferers from acute and chronic skin diseases, and also that a recognition of this fact is of great value in the treatment and hygienic management of such cases.

In this connection, also, I would particularly like to mention the frequency of what may be called the erythematous affections, such as the different forms of urticaria and nodose erythemas of the skin and mucous membranes, in sufferers from gout in its true or mixed forms. These affections present a distinctly neurotic element in their mode of onset, such as is often present in attacks of true podagra which do not give us a history of any traumatism as a determining cause. Such cases are sometimes associated with an excess of uric-acid excretion, but not by any means always. Such cases are common as the result of ingestion of certain foods, such as strawberries, apples, or of wines or beers. In fact, the extreme susceptibility of gouty subjects to prompt reactions from the ingestion of certain kinds of food constitutes one of the most delicate tests of the gouty habit—a test that may often be applied where it is impossible to distinguish a gouty blood element in cases which have been classed as purely rheumatic.

Hebra has, to be sure, asserted in regard to the urticarial affections that there is scarcely an article of diet which has not been found to be toxic in the sense of causing these apparently vasomotor disturbances of the cutaneous circulation. In my own experience the occurrence of urticaria and nodose erythemas of the skin are most commonly provoked by the articles of diet which have been found to be especially inimical to gouty subjects.

In connection with the cutaneous lesions which are so often associated with a more or less distinctly gouty and rheumatic history, I would mention, as introductory to the consideration of the common neuroses to which gouty and gouty-rheumatic subjects are liable, the so-called neurotic affections of the skin, of which general and local pruritus are types. Pruritus, though a symptom which is often associated with special derangements of nutrition due to errors in diet, is often observed in many weakened conditions of nutrition such as arise from diseases of the liver and kidney, in glycosuria, and in senile

dystrophies; it is, however, I believe, a neurosis which is very often present in gouty subjects in whom it is impossible sometimes to associate it with a definite cause other than its concurrence with other evidences of the gouty habit. Some of the most aggravated and distressing forms of pruritus, both general and local, which I have ever seen, occurred in persons who have been for years subject to gout. Such cases commonly begin as a pure neurosis, and almost inevitably terminate, through uncontrollable scratching, in acute and subacute forms of dermatitis. I believe the best authorities recognize this constitutional predisposition as the basis of a large number of skin lesions. Garrod, who is reluctant to acknowledge the close affinity of gout and rheumatism, is still inclined to associate eczema especially with gout, and psoriasis with rheumatism. Other neurotic affections of the skin, such as dermatalgias, paræsthesias, which often fall under the observation of the general practitioner, are in my experience often found to present facts in their clinical history which suggest the specific nutritional derangements which we specialize as gouty. As a striking illustration of this statement, which I think will appeal to most clinical observers, I would allude to the distressing skin neurosis which occurs in a special disorder generally recognized, certainly in its mild or benign form, as a correlative of gout, viz., diabetes mellitus.

What the explanation is of these subjective disturbances of the sensory function of the skin in gout has not been determined. Anatomical research may yet show whether they are due to a lesion in the peripheral-nerve distribution, or the organic chemist may give us more exact evidence of the presence in the blood-serum of the accumulation of uric acid or some other product of food metabolism which can be experimentally shown to be the source of nerve irritation.

Neural affinities of gout are not observed exclusively in sufferers from typical and rheumatic gout, but are observed, in my experience, among the members of gouty families who have never had any arthritic manifestations, especially, as is well known, among the females. These nervous symptoms of gouty origin are often, in women, the primary manifestations of what Trousseau long ago called larvaceous gout, so often observed at the period of the menopause. The list of neuroses which the best clinical authorities have recognized to be often of gouty origin is a long one, and includes not only

migraine, whether in its blind, sick, or aching forms; but asthma, angina pectoris, gastralgia, epilepsy, hysteria, neurasthenia, and even the transient psychoses, such as the varied forms of mental derangement, from the mild to the severe forms of melancholia and mania. What has just now been said of the determining cause of the sensory cutaneous derangements must be said also of those graver symptoms of nervous disease. They have thus far eluded the researches of the pathologist, and they go toward supporting the idea that arthritic gout itself is often largely a neurosis, and that uric acid is a coincident phenomenon of disordered chemical nutrition, the real significance of which, either as cause or effect, has not yet been demonstrated. Much might be added to what has already been suggested concerning the correlation of structural changes and functional and nervous derangements which justify a basic unity in what we recognize as gout or the gouty vice of nutrition.

I may say here that I have made no statement in regard to the sensory derangements which I have observed in gouty families which I could not substantiate, if time allowed, with illustrative cases.

There is one argument which should be briefly mentioned concerning the relationship of gout and rheumatism, which is based upon the present prevailing therapeutics of these diseases; I allude, of course, to the common and successful use in both of the salicyl compounds. In paroxysms of acute gout, in acute rheumatic fever, as well as in the subacute forms, and in functional and nervous derangements with which arthritic manifestations are often allied, there can be no question as to the conspicuous value in the majority of cases of the coal-tar derivatives. Whether these remedies act simply as anæsthetics, as has been claimed, or whether, as seems more probable, through a sort of catalytic action upon the metabolic processes by which the peccant matters in the blood in these diseases are generated, are questions still *sub judice;* but the fact of their great utility in diseases which have so many points of resemblance is certainly not without significance.

Nothing has been said of the connective-tissue lesions observed in parenchymatous organs, such as the sclerotic changes in the liver and kidney, the sclerotic degenerations in the bloodvessels and nerve-sheaths. These are especially interesting in their bearing upon the

gouty vascular complications which terminate so many lives which have had a history for years of gouty and rheumatic disease. Endocardial changes with compensatory cardiac hypertrophy, followed by the degenerative changes in the cardiac muscles and bloodvessels which lead to thrombosis and apoplexy, these all clinical experience proves are too often the final cause of the catastrophe of a pathological process which, whatever may be its determining or efficient cause, is clearly a disorder of nutrition, a disorder which is often inherited as the penalty of ancestral sins, or as the sometimes slow but sure retribution of the violation of what Sir Andrew Clark was wont to call the laws of physiological righteousness.

In thus presenting what may be regarded as a somewhat extreme view of what is called popularly the lithic-acid diathesis, it is to be distinctly understood that I have considered it wholly from a clinical stand-point. My knowledge of organic chemistry, like that of bacteriology, is practically so imperfect that I must acknowledge, in both these departments, which have already become so essential to the successful cultivation of practical medicine, that I am not entitled at all to discuss the complex questions by which the masters are still vexed, especially am I incompetent to deal with the chemical problems involved in determining the true relations of uric acid to disease. I can only consider it from the point of such physiological chemistry as I learned from the work of Bence Jones, which was done long before organic chemistry had made its great strides in enlightening the science and the art of medicine. I would say, also, that I am not unmindful that a line of thought long pursued without continuously improved illumination is sometimes apt to lead us far astray from the narrow and straight path of truth. Gout has always been a disease of personal and special interest to me in its clinical aspects, and I have erred, perhaps, in observing it with a natural leaning toward efforts to correlate diseases rather than to differentiate them; to avoid making species of varieties, or genera of species; in other words, to endeavor to apply as far as possible the principles of the study of natural history to disease.

As clinical observers, however, we believe that we are in possession of the fact that a great variety of functional derangements are frequently associated with the more objective signs of gout in the individual or with a gouty inheritance illustrated by the family history.

It is not time, we think, to assume, as we have been apt to assume, that uric acid furnishes a key to the solution of so many hitherto unsolved problems, but that as a step, furnished by organic chemistry, toward a working hypothesis which future discoveries are likely to improve, it is most worthy of consideration. Clinical observation alone, however, must be the final test of the significance and the value of the work done by organic chemistry.

It is necessary that the clinical observer of the present day should be better equipped than those of us are who were educated thirty or forty years ago, to judge with intelligence and without prejudice of the bearing of the discoveries of modern organic chemistry upon the science and art of medicine. It is a wholesome sign that the instruction in chemistry in our medical schools is so much better than it used to be, though it is still far behind what it ought to be. In all large communities there might be fewer drug-stores and one or more well-equipped laboratories with skilled investigators in control, who could furnish practitioners with the exact information in all matters requiring expert chemical knowledge, essential for the making of a correct diagnosis. Such chemical laboratories as I have suggested would accomplish for general practitioners what the bacteriological laboratories do to determine a correct diagnosis in diseases of bacterial origin. There are many questions in daily practice which require a much more accurate knowledge of the principles and technique of the chemistry necessary for the examination of the blood and excretions than is at the command of most doctors. It is only necessary to allude to the errors in diagnosis and prognosis, which are based upon routine examinations of urine, to show the importance of more accurate and scientific inquiry in this direction. In the question under discussion, for example, it is clearly impossible to determine the importance of uric acid as an etiological factor in disease until we have some trustworthy means of knowing whether the morbid conditions which have been alleged to be due to lithæmia are really uniformly and unmistakably shown to be associated with an excess of uric acid in the blood.

3. The Uric-acid Diathesis from a Clinical Stand-point.

By JAMES TYSON, M.D.,
of PHILADELPHIA.

In being asked to take part, from the clinical stand-point, in a discussion of the question, "Is a uric-acid diathesis an important factor in pathology?" I take it for granted that it is desired also that I do so as far as possible from the stand-point of personal experience. To such expectation I shall endeavor to conform. On this account it may happen also that I shall pass by some of the conditions which are supposed to illustrate the office of uric acid in the respect queried after. Should this be the case, it will be because I have not had sufficient experience with such conditions to justify their treatment at my hands. I shall endeavor, too, as far as possible, to deal with actual conditions.

At this point I will state also what I have come to regard as the sign of the uric-acid diathesis, interpreting my own observations by those of contemporary and previous observers. I regard that person as the subject of the uric-acid diathesis who secretes habitually, or more or less habitually, a scanty, high-colored urine, of high specific gravity and decided acid reaction, a urine which promptly deposits, either at the temperature of the body or at a slightly lowered temperature, a copious sediment of uric acid and mixed urates, to which oxalates may be added. Such a urine may contain a trace of albumin and even a few hyaline casts. I do not say that this constitutes the uric-acid diathesis. It is rather its sign, or perhaps one of its consequences, whence we may infer its presence. It matters not, from the clinical stand-point, whether such person ingests more uric acid, manufactures more uric acid within his organism, or does not take in enough water to hold the uric acid in solution, he is the subject of a condition which produces this result. It may also be well to say at this point that when the word uric acid

is used, not only uric acid and its compounds, but also all the oxaluric bodies of modern chemistry are intended. I will not attempt to differentiate them, leaving this to the chemical referee.

I. The most manifest of the results of this diathesis is the tendency to uric-acid *gravel* and uric-acid *calculus*, a result so commonly recognized that it is scarcely necessary to make any extended reference to it. Less manifest, though scarcely less unanimously conceded, is an irritative effect of the urine of such cases on the kidneys and urinary tract, as the result of which arises in the course of time a nephritis of the chronic interstitial type, and in the larger urinary passages a catarrhal inflammation, of which cystitis is the commonest form, a cystitis rarely of high degree.

II. It is, however, true, as already intimated, of the uric-acid diathesis, that it means something more than a scanty urine readily depositing urates and uric acid. It is something of a less tangible character. As to what constitutes this condition more precisely, I also leave the chemical referee to decide. It, however, leads to some results that are scarcely less tangible than gravel and its effects, and one of these is *gout*. Whatever may be the reasoning as to the sources of uric acid, it is commonly acknowledged that it is this substance, either within or without the bloodvessels—that is, in the adjacent tissues—which is the direct cause of true gout as constituted by an attack of podagra or gout in some other joint. It has not, however, been clearly settled whether the painful symptoms are due to uric acid within or without the bloodvessels. For although a deposit of urates in the vicinity of joints without the bloodvessels is acknowledged to be the most infallible sign of a gouty process, yet such deposits are well known, at times at least, to be absolutely painless.

The frequent association of chronic interstitial nephritis with gout is due also to the irritative effects of the same agent, which operates from within the renal vessels and superadds its effect to that of uric-acid-charged urine already referred to. This is also a matter of general acknowledgment. I do not forget that with the supervention of nephritis in gout the urine is increased, its specific gravity is lowered, and uric acid may cease to be a sediment, being held in solution by the more copious urine.

III. As undoubted in my own mind as that gout is the result of

uric acid is it that the uric-acid diathesis is frequently responsible for an idiosyncrasy in which depression of spirits is a constant symptom. Extreme modesty, a want of self-reliance, and a disposition to avoid society, in addition to moodiness, irritability, and bad temper, are a part of the same condition. To this is often added what is called biliousness, and we commonly say the liver is torpid; but when we say this we do not always have a definite notion of what we mean. It is certain, however, that there is often constipation, and the pulse is frequently slow. This, with scanty dark-hued urine and copious sediment, already alluded to, constitutes the well-known condition to which the word *lithœmia*, in its more limited sense, is applied, the word lithæmia being also used as synonymous with uric-acid diathesis. The symptoms of this well-known condition I assign to an accumulation or retention of uric acid and allied substances in the blood. This proposition has its most satisfactory proof in that which constitutes its successful treatment—viz., measures to increase the elimination and diminish the ingestion of uric acid.

IV. That uric acid is responsible for certain cases of *migraine* I am also ready to admit. I could cite many cases from my own experience which attest this, of which the following may be regarded as a type, being one tolerably well studied:

F. R., a gentleman of large means and abundant leisure, but leading an active life, consulted me when he was fifty years of age. His father had had sick headaches almost all his life, although toward the close of it they disappeared. The attacks lasted a day or two, during which he was also sick at the stomach.

Mr. R., Jr., began to have similar attacks after he was thirty years old. He would rise in the morning with a headache, which gradually grew worse, until by noon he was compelled to go back to bed. He would finally fall asleep, and sleeping until nine or ten o'clock at night, would wake and find the attack gone. The pain would be behind the eyes and in the temples, and he could stop it for a moment by yawning and by pressing the great vessels of the neck. The attacks were associated with nausea and accompanied by pains in the legs and stiffness—a sort of ache or tired feeling, with inclination to stretch the legs out. This sensation would come on rather toward the end of the attack. The next day he would generally feel uncommonly well, although there would be a little sore feeling remaining in the head. He would also have a little tenderness over the submaxillary glands when he had the headache. For five or six years, or since he was forty-five, these attacks had been so far modified that he had no nausea, which was replaced by a tendency to looseness of the bowels. Before the attacks became milder

they lasted longer, generally extending over two days. Until the last five years he perspired very little, even with active exercise, but lately the tendency to perspiration has increased somewhat. He had four or five attacks a year, and was sometimes awakened by them at night. He is very temperate, almost a teetotaler; alcohol in any quantity brings on the attacks, especially champagne. In 1873, while in England, he experienced a painful sensation in the urethra, a sensation which extended to the end of the penis.

The urine at all times was typically lithic, the specific gravity ranging from 1021 to 1032, while it deposited a copious sediment of uric acid and urates. It contained no albumin or casts, and usually no sugar, though occasionally a feeble reaction for sugar was obtained. The quantity was always small, commonly about 32 to 34 ounces in twenty-four hours. On two occasions the urine was purified by the lead process, subsequently to which sample No. 1 contained one-sixteenth of 1 per cent. of sugar; No. 2, one-fourth of 1 per cent. of sugar. Neither of the specimens contained any sediment at the time of their examination. No quantitative analysis for uric acid was ever made, but the characters of the urine were typically those described as representing the uric-acid diathesis.

After some preliminary treatment with alkalies he was ordered to use the true French Celestins Vichy as an habitual drink; never to take less than a quart a day, often more. Under this treatment the headaches grew less and less frequent, until they have practically disappeared. Mr. R. is now about sixty-five years old. It has been a year or two since I heard from him, but when I did hear from him he was in excellent health, but continues to take his Vichy as originally ordered, feeling safe as long as he does so.

By no means every case of migraine is, however, due to uric acid. It is commonly admitted that eye-strain is the cause of a large number. After this, reflex causes of various kinds, especially of pelvic organs, are active factors.

V. I believe also that uric acid in solution may be the cause of high tension *in bloodvessels*, causing contraction of the arterioles and capillaries; also that its continued presence in the blood may produce *endarteritis*, with *degeneration* and *sclerosis* of the vessel-walls, together with the accidents which grow out of such degeneration—viz., rupture and apoplexy as well as renal disease, and hypertrophy of the left ventricle. The latter I regard as partly compensatory, produced in order to make up the lost propulsive power derived in health from the contractile arterial walls.

VI. *Vertigo* in most distressing forms is also at times a result of the presence in the blood of the oxaluric bodies. It may be alone or associated with other symptoms.

In all these conditions save lithiasis and gout, and possibly in the latter also, I believe that the offending uric acid or allied substances are operating in solution through the blood, it may be in concentrated solution, but nevertheless in solution.

In the causation of the processes above described I believe that uric acid and its congeners play a decided rôle; but leaving them, we enter upon more debatable ground. Does uric acid produce rheumatism as something distinct and separate from gout? Does it produce sore-throat, asthma, and bronchitis? Does uric acid produce gastric and intestinal symptoms? Does it produce glycosuria and diabetes?

First. Does uric acid produce rheumatism as something separate from gout? At this stage we enter on a question most difficult to treat satisfactorily, indeed, impossible to discuss in such a way as to meet all objection. The chief difficulty lies in the absence of a generally accepted notion as to what constitutes subacute and chronic rheumatism. I say subacute and chronic rheumatism, because it is these as to which the difficulty lies. At the present day acute rheumatism is generally acknowledged to be an acute infectious process, and I am unable to recall from my own experience, at least, any influence of the uric-acid diathesis on its causation. I therefore omit it from my part of the discussion.

The question hinges further on the diagnosis between gout and rheumatism. Everyone who has had experience knows that there is a class of cases, not at all rare, including especially well-to-do persons past forty, in whom attacks of arthritis, and even muscular pain, succeed on errors of diet. Such a diet may include an excess of proteids, or it may be acid fruits, or wine and beer, which cause the mischief. I acknowledge that I have seen many cases of so-called rheumatism, especially muscular rheumatism, among my friends as well as my patients, who, as they grow older, have had to substitute whiskey for wine and beer, because they found the latter produced lumbago and even articular rheumatism. In some of these the urine presented the characters constituting the uric-acid diathesis; in others not. In others a gouty ancestry was their portion, or a history of an attack of true gout existed. I do not know how these causes act. Alexander Haig alleges that beer and external cold act alike in diminishing the alkalinity of the blood and driving the uric

acid out of it into the joints and tissues (*Uric Acid*, 3d ed., p. 505). There are many objections to this reasoning, and Haig's statements themselves are conflicting. Thus he says also: "The urates which cause acute arthritis are in solution, not in suspension, and they are deposited from solution later on, when they are unirritating." Again, on p. 469, he says: "When uric acid fails to be excreted it is retained in the joints and irritates them." Also, "that the absence of uric acid from the joints after death is no reason why it is not present before death." I prefer to call these cases gout rather than rheumatism, but not on such reasoning as this. Proof as to the local presence of uric acid is practically wanting. I call them gout because they fulfil the conditions of gout, either by hereditation, by the previous presence of undoubted gout, or by presenting the conditions defined by the uric-acid diathesis. I know this reasoning is not invulnerable, but I can adduce no better. The term rheumatic gout, which has recently been reapplied to some of these cases by one of our members, Dr. Rachford, seems not an inapt one. On the other hand, the term has been of late so generally associated, though with much less foundation, with that other chronic rheumatoid condition—viz., rheumatoid arthritis—that I fear an attempt to restrict it to the cases in question would lead to more confusion.

In strong contrast with these is another class of chronic cases found among the poor, in which no such cause brings on acute attacks. In these cases there is no hereditary history of gout, and there has never been an attack of gout. Nor does the urine present the characters of the uric-acid diathesis. In these cases it has not been my experience that a meat-diet interfered with a cure or causes relapses in cases in which convalescence has set in. Nor do wine and beer interfere with their recovery. On the other hand, I believe that chronic rheumatism in such forms is a disease that should be well fed, and for this class of cases I would rather have good food than medicine. My experience justifies this conclusion. It is, of course, not always easy to separate these two classes of cases. They sometimes so shade into one another from the stand-point of symptomatology that it may be impossible to tell to which category they belong, but I am sure that the latter group has nothing to do with the uric-acid diathesis as I understand it.

A word as to rheumatoid or deforming arthritis, also known as

rheumatic gout. This disease I also believe is something quite apart from gout and the uric-acid diathesis, the conditions of which are not commonly associated with it. It is a disease of definite morbid anatomy, consisting mainly in destruction of the interarticular cartilages and in new formations about the joints, associated with trophic changes, manifested most strikingly in muscular atrophy. Deposits of sodium urate constitute no part of it. It is much more closely allied to true chronic rheumatism than gout. Occurring more frequently in my experience among the poor, it is a disease of comparatively early life, setting in usually between twenty and thirty, and even at an earlier age. Acute rheumatism and gout rarely precede it, while worry, grief, and anxiety do. The studies of our member, Stewart, of Montreal, have shown that in fully 50 per cent. of cases it succeeds upon infective processes, while the nervous origin, originally suggested by J. K. Mitchell, and further elaborated by Remak and by Ord, has much to support it. It is, however, wanting the support of anatomical changes in the spinal cord, though Pitres and Vaillard claim to have found them in peripheral nerves.

Second. Does the uric-acid diathesis produce sore-throat, bronchitis, and asthma? So far as these conditions are associated with the requirements of the gouty diathesis, it may. But there is no proof of it, except that derived from analogical reasoning. It is *prima facie* unlikely. Yet if they occur in persons who are hereditarily gouty, who have had true gout or fulfil the conditions of the gouty diathesis, and are not otherwise explainable, they may be thus caused. On the other hand, there is nothing so peculiar in their symptoms that a diagnosis of gout dare be made from the presence of such sore-throat, bronchitis, and asthma. The same is true of numerous other conditions ascribed to gout, such as the gastric neuroses, what is known as gout of the stomach, gouty diarrhœa, and the like. Their relation to the uric-acid diathesis is an assumption justified when the conditions named are fulfilled, but there is nothing in these conditions themselves which is in any way distinctive of indicative gout, or of the uric-acid diathesis.

With epilepsy depending in any way on the uric-acid diathesis I have no experience, nor with neurasthenia, alleged to be due to the same cause.

Now as to the relation of uric acid and diabetes. It is one of the

best-recognized clinical features of the latter that uric-acid sediments are frequently found in diabetic urine. But here the resemblance between typical diabetic urine and the urine of the uric-acid diathesis ceases. For, although the specific gravity of diabetic urine is high, yet it is high not from the presence of uric acid and urates, but from sugar, and, instead of being scanty as the urine of the uric-acid diathesis, it is copious. I have always regarded the sediments of uric acid in diabetic urine, which, by the way, are almost always limited to the early stages, as a result of the rather marked acidity of these urines, which decomposes the urates and deposits the uric acid.

On the other hand, it cannot be denied that there is a certain relation between diabetes and gout, shown by the fact that at times these two affections are present in the same subject, either successively or simultaneously. Most frequently, perhaps, the gouty patient acquires glycosuria and the gouty attacks may cease. In other cases attacks of gout and glycosuria alternate. In other cases still gout and glycosuria are simultaneously present. Least frequently, gout supervenes on diabetes. A case illustrating the first category has been under my care nearly twelve years. It is accompanied by a mild degree of interstitial nephritis. It is, moreover, commonly conceded that these cases are almost invariably of the mild form, easily controlled, as a rule, by a dietetic treatment only. In my experience, the number is not as large in this country as it appears to be in Germany, England, and France, or as noted at least at the Spas where diabetics and gouty patients resort. Furthermore, I believe that a certain number of cases are supposed cases; by which I mean cases in which the reduction of cupric oxide is due to uric acid and allied substances, and not to glucose. This is such a frequent event in my experience, and I so often find mistaken conclusions drawn from it, that I am of late confident it is true. Admitting, however, the occurrence of gout and diabetes in the same person in some one of the ways described, does it follow that uric acid is the cause of both? On no grounds except the reasoning of Haig, that what he calls uricacidæmia, or an excess of uric acid in the blood, due largely to its alkalinity, causes enlargement of the liver, derangement of function, and consequent glycosuria. Gout and diabetes are both nutritional disorders, and may be the result of the same cause, but that cause is not uric acid in the case of glycosuria.

This is further seen in the absence of like consequences of the two diseases. Nephritis is a very common affection in gout, manifested almost exclusively in the granular atrophic form, and very rarely the same form appears in diabetes; but it is only in the obese and gouty and in the last stages of the disease in these that it is met. The renal changes which may be said to be so characteristic of diabetes are functional and hypertrophic, the result of extreme work thrown on the kidney in eliminating the water, sugar, and salts. These are never found in gout.

Cardiac changes are rare in diabetes. When present they are hypertrophic, but moderate. They are very common in gout and of the same kind. In both diseases they are probably due to the same cause—viz., extra work thrown upon the heart, partly to overcome irritative contraction of the bloodvessels, to which is superadded in gout arterial sclerosis. The latter is very rare in diabetes except in the form associated with gout. The irritant in gout is uric acid and its congeners; in diabetes, sugar, acetone, and similar substances. These may rarely be a cause, too, of arterial sclerosis occurring late in diabetes. When sclerosis is present, as already intimated the cardiac hypertrophy is partly compensatory. When sclerosis occurs early it is a question, as suggested by Van Noorden, whether it is not primary, possibly of syphilitic origin, and itself the cause of diabetes through nutritive disturbances in the pancreas and nervous system. Finally, the very fact that when the uric acid factor asserts itself the diabetic subsides, and *vice versa*, is, in my judgment, a strong point against uric acid being the cause of both.

Admitting, therefore, as every one must, a somewhat intimate relation between the two conditions, it would seem at present that we must admit, with Van Noorden, who has given us, by general acknowledgment, the most satisfactory treatise on diabetes yet written, that an insight into it has not yet been vouchsafed us.

DISCUSSION.

DR. C. A. HERTER: Perhaps I may be permitted to say a few words with reference to certain observations made during the past seven years in regard to the excretion of uric acid in health and disease. In these observations the Ludwig-Salkowski method of determining the uric acid was exclusively used. This method, as is well known, is exceedingly accurate and gives good results. It was chosen because it afforded the likelihood of being able to make comparisons between the different urines examined in going over the results accumulated. The older methods, like the one used by Haig, are entirely unsuitable for accurate work. A large number of the cases studied were patients suffering from digestive disturbances of various kinds, gout, rheumatic affections, diseases of the kidney, epilepsy, migraine, and chorea. With these were contrasted the results obtained from the study of vigorous adults who were without any symptoms whatever.

The first thing that struck me as of importance was the fact that the majority of healthy adults upon a mixed diet showed no very wide variations in the excretion of uric acid from day to day as compared with the excretion of urea. I may say it is very exceptional to find normal adults that show a larger amount of uric acid in the urine than 1 to 40, or less than 1 to 60 of urea. It was found that in contrast to these normal excretions of uric acid there is a very large class of patients who excrete very much more uric acid than I have mentioned—patients whose uric acid bears a ratio of 1 to 30, 1 to 20, or even 1 to 15 of the excretion of urea. It was found, furthermore, that there was nothing characteristic in the clinical conditions present in these patients. The greatest variety of conditions showed a very marked increase of uric acid as measured by this particular standard.

In many instances the uric acid increase seemed to be related to acute disturbances of digestion. In other cases the condition was a chronic one, and continued from month to month. I am inclined to think that the condition that is most generally associated with a marked continuous increase of the uric acid of the urine is some form of derangement of digestion, and think that this accounts for the great majority of cases in which a uric acid increase is present. It may not, perhaps, account for the increase that is observed in some paroxysmal conditions; for instance, in epilepsy. In pneumonia there is a marked increase of uric-acid excretion after the crisis, and so there is in migraine; but in the latter case perhaps there is a relation to disturbed digestion, though one cannot feel sure of it.

The point I would emphasize here is that there is nothing particularly characteristic about a distinct increase in uric-acid secretion, and there is no reason for connecting it with any particular clinical form of disease unless it be some form of digestive disorder. These patients who during long periods of time excrete increased amounts of uric acid are likely to have that still further increased by any sudden derangement in the digestion. An indiscretion in diet, the use of alcohol and of certain drugs, especially salicylate of

sodium, is likely to give rise to a marked increase in these persons beyond the increase already present. I am disposed to look upon this susceptibility to an increased excretion of uric acid as the result of trivial influences, such as fatigue, excessive mental worry, etc., as the characteristic feature of uric-acid diathesis. It seems to me that if we are to use the term uric-acid diathesis in any legitimate sense we should use it strictly in this limited way.

The idea has been referred to to-day that it is a characteristic of the uric-acid diathesis that patients excrete a small amount of urine, of high specific gravity and high acidity. That is true in many cases, but it is not characteristic, for the amount of uric acid may be increased in urine that shows quite opposite features from those mentioned. The increased amount of uric acid in the urine is no evidence of an increase of uric acid in the blood. A great many errors have arisen from supposing that this was really the case. The work of Herbaczewski is certainly the most suggestive that has been done in reference to the origin of uric acid, and enables us to consider the uric-acid question from a biological stand-point. It seems upon the whole likely that there is a certain relationship between leucocytosis in general and the increase in excretion of uric acid. There are many evidences of this relationship, but I am inclined to agree with Dr. Vaughan, that it is not an absolute one. In many cases there is no leucocytosis where there is marked uric-acid excess, and I think that there may be other sources of uric-acid production than the nuclear degeneration of hyperleucocytosis. It would be peculiar if the production of uric acid were limited to one particular set of cells in the body.

So far as the question of attributing the symptoms of disease to uric acid is concerned, it seems to me from a review of the literature of the subject, and some observations upon it, that there is absolutely no evidence at the present time that any pathological condition whatever is caused by the accumulation of uric acid in the blood. The only ground we have to suspect it of being the cause of disease relates to the mechanical conditions referred to by Dr. Vaughan. Repeated examinations of the blood in various conditions of disease have, I think, failed to reveal any actual increase of the uric acid in the blood, and in the absence of such evidence it would seem to be going out of the way to charge these conditions to uric acid itself. With an increased excretion of uric acid there are frequently associated morbid digestive conditions that may be the real cause of symptoms. I look upon increased uric-acid secretion as a terminal metabolic condition due to some antecedent derangement, instead of considering it as a causative factor in disease. The direction in which we should look for such antecedent derangement is in the changes occurring in the intestine as the result of abnormal fermentation and putrefaction. We know that a great variety of toxic agents may stimulate the excessive formation of uric acid. The subcutaneous administration of Witter's peptone albumose may do it, and there are other substances which will do the same.

There are certain difficulties in the way of accepting the Herbaczewski theory just as it stands. I have studied the blood, and never found any

increase of uric acid there, even after removal of the kidneys from animals. That fact remains to be harmonized with the theory.

In regard to treatment, it occurs to me that we are wrong in treating these conditions by medicines and drugs alone. It is true that quinine and other antipyretics have been supposed to decrease the excretion of uric acid, but we cannot make use of these drugs for any length of time in the treatment of chronic conditions, and we must rely upon change of diet, rest both bodily and mental, out-of-door life, etc. It has interested me very much to observe how many persons there are who toward spring become worn out, easily fatigued, and irritable, and who show at that time a marked increase of uric acid in the urine. Send such patients to the country for a few months, under favorable conditions, and then examine their urine, and you find the amount of uric acid has gone down very much indeed. One of the phenomena frequently associated with an increase of uric acid, and which deserves a special study, is the acidity of the urine. Where uric acid is excreted in excess for a long period of time, the acidity of the urine as measured in terms of oxalic acid is frequently much increased. Though we know nothing positive to-day I am inclined to think it stands in some significant relation to nutritive troubles. One of the most remarkable things about the kidney is its ability to produce an acid secretion from the alkaline blood plasma. This transformation is not at all understood by physiological chemists, and we have here, I think, a line of investigation that may throw some light upon a great variety of conditions which we have been attributing to uric acid.

The theory of the causation of uræmic conditions with high arterial tension, by uric acid, seems to me to be utterly without basis. I have in such cases obtained blood and studied it with great care by the Ludwig-Salkowski method, but have never been able to obtain any uric acid whatever. Until we can find the uric acid in the blood it is unwise to speak of the toxæmic conditions due to uric-acid excess.

DR. A. H. SMITH: It seems to me that the discussion to-day has illustrated very markedly the error we are likely to fall into when we endeavor to make the results of reactions in the test-tube tally with the reactions that take place in the body, leaving out of the question the problem of vitality. Dr. Herter refers the output of uric acid to causes that cannot operate except through the nervous system, and we find them running through a great variety of conditions; for instance, glycosuria is determined very often by mental causes, such as fright and great worry; and while I am far from depreciating the value of chemical research in this direction, I think it must always be checked by the question how far it should be conditioned by the vital changes which are constantly going on in the body. Early in my professional life I adopted the idea that uric acid in the body was due more to the ingestion of the carbohydrates than to nitrogenous food, and the whole of my clinical experience has tended to confirm that view in my mind. Of course, in England we find gout associated with the eating of beef and mutton—that is, albuminous diet, and whether there is a difference in the observations in this

country, I cannot say, but my own observation agrees with what Dr. Draper has said, that the source of this difficulty is oftener the use of sweets and starches than it is proteids.

One of the worst cases I ever saw, a case in which spontaneous amputation of the big toe took place from accumulation of chalky material in the joint, had been under treatment for a long time by drugs calculated to relieve a gouty condition, recovered absolutely within a few months by simply putting the patient upon a diet similar to what we would use for cases of glycosuria. I have seen so many similar cases that I am inclined to believe it more likely to be the determining cause than is a proteid diet.

I have under observation now a lady who suffers alternately from stiffness and discomfort of the small joints when she uses largely starchy foods, of which she is particularly fond, but who has prompt suppression of the trouble upon change of diet and without any medical treatment whatever. If she carries it to the other extreme, however, she suffers from the want of heat-producing food, and complains of cold extremities, etc.

It seems to me there is some support for the idea of suboxidation which Dr. Draper seems to have abandoned. Some years ago I undertook to study the relative output of urea and uric acid of patients who were getting an unusual amount of oxygen by inhalation. We may say oxygen is not taken up by the system in that way, but I believe it is to a certain extent. I found in many cases that patients inhaling increased amounts of oxygen with the air certainly gave a smaller output of uric acid as shown by its diminished deposit from the urine. At any rate we found the influence of out-of-door life with better opportunities for the inhalation of pure air to be one of the best correctives we have for this uric-acid condition.

The subject of discussion to-day is the uric-acid diathesis, and I suppose we intend to express by that the clinical picture we have all along designated in that way, though, according to Dr. Herter, we must now dissociate it from the presence of uric acid in the blood.

DR. F. C. SHATTUCK: I would like to ask Dr. Smith what method was used in determining the proportion of uric acid to urea in the cases in which oxygen was inhaled?

DR. SMITH: I cannot say now, for it has been so long ago that I have forgotten the details.

DR. SHATTUCK: I am told by chemical friends that it makes a great difference what method is used for this test. The method of which Dr. Herter spoke, the Ludwig-Salkowski is considered perfectly trustworthy, whilst that used by Haig is not productive of as good results.

DR. C. G. STOCKTON: There is just one point in the discussion that I would like to touch upon in substantiation, clinically, of what Dr. Herter has said as to his conclusions from chemical research. It seems to me very remarkable that there has been seen the improvement in these cases under a diet that would apparently make the most uric acid. For years I have been

much interested in these cases, and have seen the results that Dr. Draper has described. It has been my opinion that the improvement occurred not because these substances carried less uric acid into the body but because they were imperfectly digested. If one studies carefully the digestive tract he will find proof for what Dr. Herter has said, and I think the explanation given may do away with the apparent discrepancy. There are cases of so-called lithæmia made worse by the meat diet, and in such the digestion of albuminoids will, as a rule, be found faulty.

DR. C. A. HERTER: I would like to say in reference to Dr. Smith's remarks that while I made no observations of the kind he spoke of, I have made some upon the opposite condition of affairs—the condition seen where the patient is suffering from an organic lesion of the heart and is extremely cyanotic. One would expect such patients to show an increased excretion of uric acid if deficient oxidation were the cause; but that does not appear to be the case. These patients are like normal persons in respect to their excretion of uric acid. This observation has also been made by Van Noorden and others.

I would like also to say a word about the influence of milk in reducing uric-acid excretion. It seems to me that the food most likely to be well digested without excessive fermentation is that form most likely to be followed by a drop in any excess of uric acid. The use of milk as a diet is usually followed by a very sharp drop in the ratio of uric acid to urea. In a healthy man upon a milk diet the ratio is normally found in about 1 to 80. When a patient who is excreting uric acid in the proportion of 1 to 30 of urea is put upon a milk diet there is a drop to 1 to 40 or 1 to 60, and this is, I think, almost regularly the case. This fact contains an important therapeutic suggestion.

DR. A. JACOBI: I have no theory to suggest and no explanation to give, but I wish only in a few words to relate a case in connection with the paper of Vaughan. A lady, about thirty-four years of age, rather stout and short, was sick all last summer with some fever and digestive troubles. When I first saw her, at the end of November, she was having movements every three or four days, which sometimes looked as if they had gone through a constriction; they were tape-like. The urine was of a high specific gravity, as high as 1034, and contained uric-acid deposits frequently, and always plenty of urates; no albumin. At one time her abdomen was so swollen that ascites was suspected. The first thing done for her at that time was to give purgatives, which relieved her to some extent, but she still felt weak and would not go out. About that time it was discovered that there was constant pain about the bones of the lower extremities. The femora were tender, and the tibiæ very much so. Pressure was almost unbearable, the pain more marked when deep pressure was made, so that it was thought there was a chronic form of osteitis. An examination of the urine showed albumose to such an extent that the test-tube was two-fifths full even after twenty-four hours standing. That remained so as long as she had the pain about the bones, which lasted several months. There was not a single specimen that did not contain

a large amount of albumose, and it increased whenever the pain increased. The blood at that time was found to show leucocytosis; about 4,500,000 red blood-cells and 15,000 to 16,000 leucocytes. Since the pain has disappeared, now about four or five weeks, there has been no albumose, and the leucocytosis is diminished.

I thought I would relate that case in this connection, because Dr. Vaughan spoke of the connection of leucocytosis on the one hand and albumose on the other with the presence of urates and uric acid. In my case I was of the opinion that both leucocytosis and albumosuria depended on the condition of the bones; a deep-seated abscess or a malignant tumor could be excluded after careful and repeated examination. It is, however, quite possible that the excess of uric acid and urates is at the bottom of it all. Indeed, the specific gravity of her urine is now from 1016 to 1018. Still, it is also true that at the same time the sensitiveness and slight swelling of the bones, particularly the tibiæ, have also disappeared in the patient, who is now practically well.

DR. VAUGHAN: I have nothing to say except that in regard to milk, the paranuclein of this food cannot yield uric acid, and that is probably one of the reasons why it is good in this form of leucocytosis.

DR. DRAPER: I have nothing to add except, perhaps, a word in regard to Dr. Smith's suggestion that the effect of a diet of carbohydrates is one of the causes of aggravation of gout in some people. That plan of dietetic treatment is one that I formulated many years ago when I found from practical experience that the diet which best suited sufferers from lithic-acid diathesis was the diet best suited for glycosuria, and that has practically been my guide in the treatment of so-called lithæmia for many years. I have been interested in what some of you may have seen in the English journals, that the dietetic treatment of gout is evidently undergoing some change in England, where they have up to the present time, I may say, regarded a diet that excluded nitrogenous foods as the proper diet for gouty subjects. I have noticed several indications of late that some English practitioners have discovered that the surest way to treat successfully some of the most aggravated forms of gouty disease was to feed the patients liberally with such foods and restrict them in the use of the carbohydrates.

DR. TYSON: I wish only to reiterate what I tried to make plain, that I do not think we really know in what a uric-acid diathesis actually consists, and the conditions mentioned I regard only its signs. We certainly have at times a concurrence of these conditions with certain symptoms which are reasonably assigned to them. It seems to me that modern chemical studies help us very little in one way or another. The essential proof of the uric-acid diathesis is to show that there is more uric acid in the blood, and I do not know that anything has been done to show this since Garrod's original experiments with the thread, and I do not know that anybody has repeated these experiments successfully since Garrod's time.

ON THE CONGENITAL HYPERTROPHIC STENOSIS OF THE PYLORUS IN INFANTS.

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In the medical literature of this country there are on record, as far as I can see, only four cases of congenital stenosis of the pylorus in children, and two of these are described by Ashby,[1] of Manchester, England. However, there are sufficient reasons to believe that this affection is not as rare as it would seem to be, judging by this scarcity of record. In the European medical literature of the last few years we see a constant growth in the reports of these cases. In 1896 Finkelstein[2] collected 11 cases, and in 1897 John Thomson[3] gives a résumé of 16, not including 2 cases of Henschel,[4] and now 4 new cases are to be added, 1 by Schwyzer,[5] 2 by Ashby,[1] and 1 by Rolleston and Hayne.[6] Furthermore, an analysis of these cases shows that they can hardly be taken as a fair representation of the actual occurrence of this form of disease.

The first case on record was described by Williamson[7] in 1841, and the second was reported by Davoski,[8] 1842. Then a period of forty-six years elapsed with no reference to this affection, until, in 1888, Hirschsprung,[9] of Copenhagen, inaugurated the present new series of records. Again, in this new series, we find that 2 cases are reported by Hirschsprung, 4 cases by Finkelstein and by Gran[10] from Heubner's clinic, 3 cases by Thomson, 2 by Schwyzer, and 2 by Ashby; each group of cases being observed by the respective writers only within a short period. This shows that if the attention of an observer was once called to the existence of this affection he did not fail soon to discover another case.

A few years previous to the publication of Hirschsprung the subject of congenital stenosis of the pylorus had been treated by Landerer[11] and by R. Maier.[12] The latter has published 31 cases (including 10 of Landerer) of stenosis of the pylorus, which were collected in the autopsy-room within the course of only a few years. They considered these cases as congenital, on the ground that there were no signs of a pathological state (catarrh, ulcer, etc.), which could have caused the hypertrophy and stenosis of the pylorus. However, as the youngest of these cases in which the stenosis was observed was twelve, and the oldest eighty years, the assumption of these authors, that the stenosis was not acquired, was not beyond doubt, and as the reports of Williamson and Davoski were forgotten long ago, it remained still an open question whether congenital stenosis and hypertrophy really occur. And herein lay the incentive for the report of Hirschsprung. The observation of stenosis and hypertrophy in a child only thirty days old brought the requisite proof that these conditions may indeed be congenital.

Now the 22 cases of congenital stenosis in infants which we find in the literature have all been found at autopsies, and in only 4 of these cases the correct diagnosis was made *intra vitam.* But in the light of the statements of Maier and Landerer, who consider the stenosis in their cases as congenital, we must assume that some of these cases of congenital stenosis of the pylorus survive not only infancy but attain sometimes even a higher age; then the expectation is justified that an early recognition and proper treatment of these cases might be instrumental in saving the lives of some of these infants. And, indeed, there are already 4 cases on record where the proper diagnosis was made, and by means of efficient treatment the children were kept alive. It is worth mentioning that 3 of these children were under the care of Heubner,[13] from whose clinic 4 autopsies of this kind were reported, and 1 of the cases comes from Henschel, who reported 2 autopsies. We may also add here, that in the few cases with autopsies in which the condition was recognized during life, the respective physicians, it seems, were enabled to make a proper diagnosis by having seen previous autopsies of this kind of cases. Thus Thomson made a correct diagnosis in his third case, Schwyzer in his second, and Finkelstein after having seen the cases of Gran and Heubner's clinic.

This brief review teaches us that the cases of congenital stenosis of the pylorus are by no means very rare, and that the mere calling of attention to the existence of this disease was often instrumental in bringing out more such cases,* and in some instances it enabled the physicians to make an early diagnosis and even to save the life of the little patients. With these considerations in my mind, I ask your permission to report here and discuss in detail a case of stenosis of the pylorus in an infant of six weeks, in which I was fortunate to see my diagnosis confirmed by an autopsy *in vivo*, but I regret to be also able to demonstrate to you now the correctness of my diagnosis by a remarkable anatomical specimen.

L. K. was a well-developed plump baby when she was born, on December 10, 1897, from a nervous, pale, and thin mother and a healthy father. I was called to see the child three days later. She was constantly crying except when she took the bottle, which she drank hastily and with unusual eagerness. The mother had no nipples, and the child was fed with milk and water, 1 to 4. She vomited occasionally, immediately after drinking, the milk being yet uncurdled; the bowels were evacuated by oil and by calomel. There was blennorrhœa of the right eye. I advised to feed the baby with smaller quantities but at regular intervals, and prescribed hydrochloric acid and aqua laurocerasi, to be given before each feeding. This had a favorable effect, the child was resting better, drank from the bottle with less haste and retained it. I was next called about three weeks later, on January 2, 1898, and was told that the medicine had been given for some time and then discontinued, the condition of the child appearing to be satisfactory. But meanwhile the nipples of the mother's breast were drawn out and the child was put to the breast; soon after the vomiting commenced again, and more than before. At the time when I was called the baby was vomiting every time immediately after taking the breast, the milk was curdled and the vomit smelled strongly acid; the movements of the bowels were retarded. The child was again very restless, cried constantly, had hardly any sleep, and baby and mother looked quite worn out. I stopped the mother's nursing, washed out the baby's stomach with warm saline, and gave calomel, which was retained and had a good effect. The baby now received only oatmeal water, the first day one ounce, and in the following two days two ounces, every hour. Before each nursing the child was given some bicarbonate of soda and cerolaurel water. The child now retained all that it was given, the bowels moved spontaneously, the heretofore diminished diuresis increased again, and the baby again rested better.

Meanwhile a promising wet-nurse was procured, and on January 6th the

* A well-known gentleman from Boston informed the writer that while listening to this paper he became convinced of having had a case of this kind under his observation.

child was again put to the breast. The baby took it with eagerness, drank hastily, emptied one breast in a few minutes, and soon vomited apparently all that it had swallowed. This occurred every time when the child was put to the breast. Supposing that the eagerness and haste with which the child took the breast might have been the cause of the vomiting, the milk was withdrawn by a pump, and then given to the child slowly and in small quantities. I had also changed the bicarbonate of soda to hydrochloric acid. At first the new arrangement seemed to work favorably; child vomited only once in five to six hours, the milk came up only in small quantities, contained flocculi of small curds, and had no abnormal odor or appearance. It was now attempted to increase gradually the quantity given at one time; but within a few days the vomiting also gradually increased in quantity and frequency. I attempted to empty the stomach by a Nélaton catheter at a time when the child, accidentally, did not vomit for a few hours, and found that the quantity which was thus removed was about equal to the amount which the child had taken within the last few hours.

When now I examined the abdomen I found the empty stomach rather strikingly contracted, easily palpable, like a little tumor, and lying in the middle line, high up in the epigastrium. There was then no atony of the walls of the stomach; nevertheless, it harbored a large quantity for hours without being able to empty it into the intestines. For the first time now it dawned upon me that I might have to deal here with a high degree of stenosis of the pylorus, and started out to establish this diagnosis by proper methods.

The following data were gradually collected within the next few days. When the stomach was filled with water under moderate pressure the entire epigastrium bulged up, and on percussion the dulness of this region terminated about one finger above the umbilicus. The bulging upper part of the abdomen contrasted sharply in appearance with the sunken lower part. When the stomach was moderately inflated with air the contrast between the upper and the lower part of the abdomen was still more striking, and the stomach seemed then to reach the umbilicus. When the stomach was filled with water and the colon inflated by air it was easily seen that the stomach was lying just next to the wall and the colon beneath it. When the stomach was filled with water, or during and after nursing, peristaltic waves could distinctly be seen passing over the region of the stomach from the left to the right side. While the child was quiet the lower end of the soft catheter, when pushed deeply into the stomach, could be felt bent around and running alongside the large curvature, marking in this way the lower border of the stomach (method of Boas). When there was some liquid in the stomach and air was blown through the catheter, the air which escaped from its inside opening into the surrounding liquid caused a gurgling sound; the auscultation of this sound was utilized to locate the lower end of the catheter and with it the lower border of the stomach. By these latter methods, and by percussion, the size of the empty stomach could be established, even when it remained permanently relaxed, which was, indeed, soon the case.

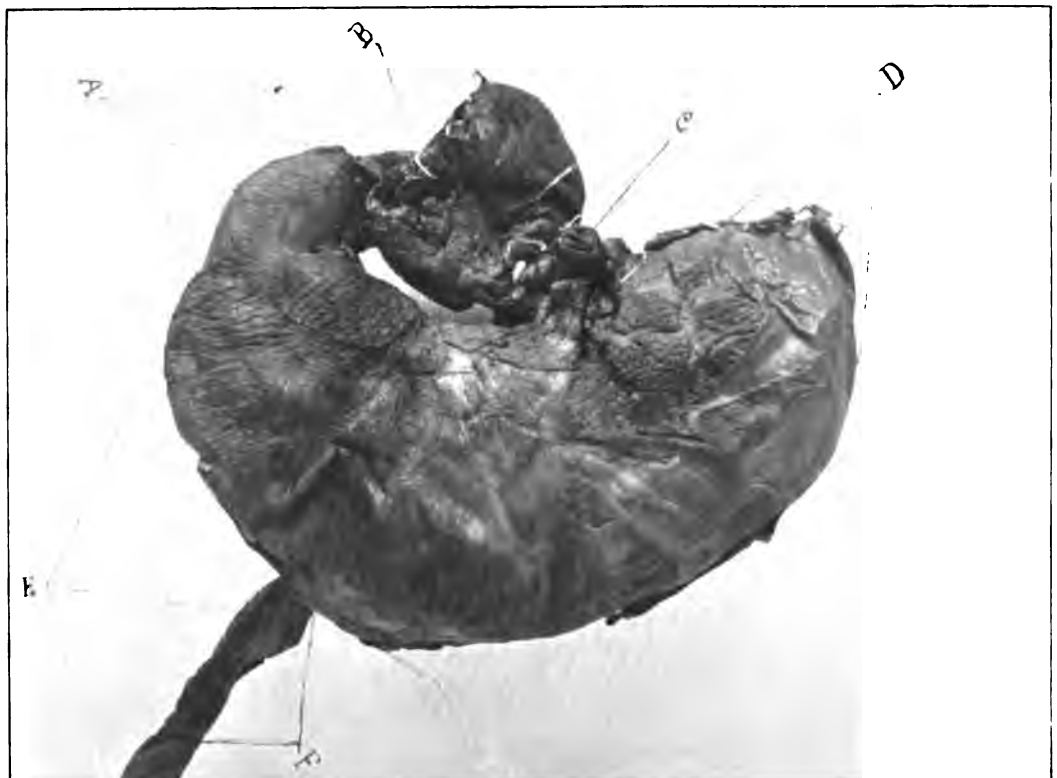
The tumor-like contraction which is mentioned above was observed only twice in the beginning of the scrutinizing examination. In the consecutive period it was found that the stomach remained relaxed, even in a thoroughly empty state, and that gradually it assumed larger proportions. It was then evident that there was a serious degree of stenosis of the pylorus which gradually brought out a hypertrophy and dilatation of the stomach.

We started now to wash the stomach daily, which revealed at the same time the fact that even violent and frequent vomiting attacks never thoroughly empty the stomach.

As we had to settle now for a permanent state, we had to let the nurse give the child the breast directly, as she was unwilling to continue the feeding by the previous methods; it was nursed very frequently, but only for a few minutes at a time. The movements of the bowels were very retarded, but promptly responded again to a dose of calomel, which seemed to show that there was still some free communication between the stomach and the intestine. The mixture of the hydrochloric acid and the aqua laurocerasi was discontinued, fearing especially the paralyzing effect of the latter on the contractility of the stomach. The extreme restlessness of the child, however, necessitated the resumption of the latter drug again, but very small and infrequent doses were sufficient to keep the baby in a tolerably tranquil state. For a number of days the condition was a tolerable one; the child was resting, vomited only four to five times a day, passed sufficient urine, the bowels moved once or twice a day. On the 17th, 18th and 19th of January the stomach was not washed. It was noted by the family, with satisfaction, that on these days the child vomited less than before. On the 20th, however, it was found that the child had meanwhile lost a few ounces in weight, that she urinated very scantily, and was again constipated. An examination of her abdomen showed that the stomach now extended far below the umbilicus, and the peristalsis was nearly entirely absent. The stomach was now emptied by a catheter, and it was found to have contained eight ounces of curdled milk mixed with some tenacious mucus. A renewed attempt to wash the stomach more frequently brought no perceptible change in the now quite hopeless state.

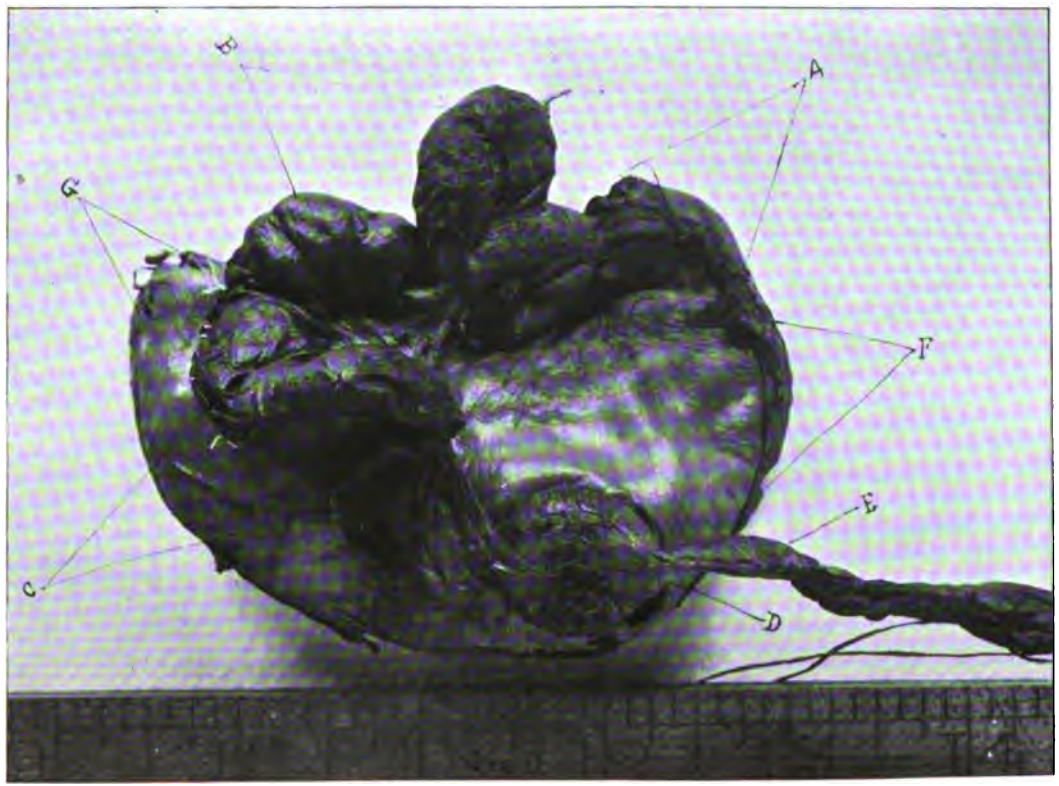
It was then decided to attempt to help the child by means of an operation. The child was still in a tolerable state, was not emaciated, and offered a fair chance to stand operation. This was done on the 23d of January by Dr. Willy Meyer. The child was then forty-four days old. The operation lasted about forty-five minutes; the baby stood anæsthesia fairly well (Schleich's mixture); hypodermatics with stimulants were freely administered. As soon as the abdomen was opened the very large stomach filled with air presented itself. It had already the configuration and the position of the stomach of an adult. The walls of the stomach, especially of the pyloric part, appeared to be thickened. The pylorus itself offered a striking appearance: it looked like a little tumor of the size of a large cherry, uniform in all dimensions. The intestines appeared to be totally empty; the surgeon then quickly performed gastro-enterostomy by means of a Murphy button of the smallest size

PLATE I.



Stomach of L K., hardened in alcohol; anterior aspect. A. Hypertrophic pylorus; B. Dilated duodenum; C. Cardia; D. Fundus: E. Pyloric portion; F. Distal end of jejunum.

PLATE II.



Stomach of L. K.; posterior aspect. A. Pylorus; B. Dilated duodenum; C. Dilated jejunum; D. Seat of Murphy-button; E. Distal end of jejunum, showing natural diameter; F. Pyloric portion of stomach; G. Fundus.

he could then obtain. The baby appeared, after the operation, in a tolerable state; hypodermatics were continued; an attempt at transfusion was unsuccessful on account of the minuteness and emptiness of the infant's vein. A few hours after the operation, however, the child started vomiting small masses of brownish-black color; this was followed by frequent tremors, which gradually developed into convulsions. The temperature rose to 103°, and, although convulsions and fever subsided after some time, the child gradually collapsed and died thirty hours after the operation. The child vomited no bile, and the diagnosis was correctly made before death; the button was too large for the extremely narrow jejunum, and not only prevented the stomach from emptying its contents into the intestines, but also caused a stagnation of the bile in the parts of duodenum and jejunum lying between the pylorus and the place of the anastomosis with the stomach. (I shall here remark that the infant never during her short life vomited bile, and also that she never vomited at any other time except immediately after drinking.)

The autopsy was restricted to the abdominal cavity. There was no trace of inflammation. All the intestines were absolutely empty; no other abnormalities presented themselves. The stomach, with the part of the intestines connected with it by means of the Murphy button, was removed. The stomach is of remarkable size; it measures from the outer end of the fundus to the pylorus 11 centimetres. The fundus is already well developed; its walls are thin, but the walls of the pyloric portion are quite thick. This portion is funnel-shaped and ends into a fine opening leading into the pylorus proper, the walls of which are considerably hypertrophic, and the lumen only permits the passage of a fine probe less than one millimetre in thickness. The narrow channel, which is not straight, but presents rather a broken line, was obliterated with tenacious mucus. The peculiar appearance of the thick duodenal end of the pylorus with the tenacious mucus hanging from it strikingly reminded one of the vaginal portion of the uterus protruding into the vagina. The contrast between the hypertrophic pylorus and the very thin-walled duodenum is there the more sharp, as duodenum and jejunum there present the striking example of acute dilatation, due to the stagnation of the bile within them during the period elapsed between the operation and death. (See Plates I. and II.)

Professor T. M. Prudden, who kindly examined the specimen, made the following report: "On a longitudinal section of the pyloric portion of the stomach in the line of the greater curvature and extending into the duodenum, the pylorus (hardened by formalin followed by alcohol) measures from the tip of the gastro-duodenal valve to the point at which the pyloric portion rather abruptly merges into the general stomach wall, 3.5 cms.; the thickness of the entire wall just back of the tip of the gastro-duodenal valve is 4 mm. Passing backward toward the stomach the wall gradually thins until, at a point 7 mm. from the tip of the valve, it measures 3 mm. It then gradually thickens, maintaining for about 1 cm. an average thickness of 4

mm.; then thins abruptly to merge into the general stomach wall. The mucous membrane is thrown into a series of longitudinal folds.

"The *microscopical examination* shows that the thickening is largely due to the presence of dense fibrous tissue in the submucosa and to a hyperplasia of the inner muscular layer, especially of the proximal half of the pyloric portion. The moderate thickening of the wall at the gastro-duodenal valve which gives to this structure an undue prominence when seen from the duodenal aspect, appears to be almost wholly due to the fibrous hyperplasia in the submucosa; while at the other—the proximal end of the pyloric portion—both the inner muscular layer and the submucosa share in producing the thickening of the wall. The external muscularis presented no abnormality. The mucous membrane was not sufficiently well preserved to permit the detection of any abnormality save a general slight encroachment between the bases of the glands of the hyperplastic tissue in the submucosa.

"The *anatomical diagnosis* is accordingly stenosis of the pylorus, from fibrous hyperplasia of the submucosa; hyperplasia of the inner muscular layer, especially of the proximal half of the pyloric portion of the stomach."

When we recapitulate briefly the main features of the case we see that in the first two weeks there were no other symptoms except restlessness and extreme eagerness for drinking, with occasional vomiting. But this soon became very frequent, and continued so until a few days before death. The vomiting was always accomplished with force; it always occurred soon after drinking, and at no other time; the vomit never contained bile and did not show any fermentation or other signs of a catarrhal condition of the stomach. Until a few days before death the bowels moved tolerably fair and responded promptly to calomel. A study of the dimensions and contractility of the stomach has demonstrated that at the beginning of the fourth week, when the examinations were first begun, the stomach was rather unusually contracted when empty and showed lively peristalsis when full. Gradually, however, apparently a state of atony of the stomach developed, it became more and more permanently dilated, extending over the larger part of the abdomen with no more peristalsis in sight. And just at this juncture the vomiting seemed to diminish, but with no sign of food passing into the intestine or being absorbed from the stomach; there was no defecation and but little urination, and the child commenced to lose weight.

That the extreme narrowness of the lumen and the remarkable hypertrophy of the walls of the pylorus were not acquired within the very short period of the child's life, goes without saying; there are no

signs of an ulcer, an inflammation, or of anything else which could cause such a stenosis and hypertrophy. The stenosis was there from the very first; it was congenital. Nevertheless, from the beginning to a few days before the end food doubtlessly passed through this extremely narrow channel from the stomach into the intestines, at least in such a degree as to enable the body to keep up a metabolic equilibrium. There was no loss of the original weight. Then there were passages from the bowels of fecal masses, and calomel has always shown its unmistakable effect. Surely contents of the stomach managed to get through the pylorus with a lumen of less than 1 mm. in diameter. It is a remarkable fact; but has illustrating parallels in the autopsies reported by Landerer and Maier. The following instance (Landerer) is very instructive: In a man of forty-five years, who died of marasmus, an enormous stomach was found in which the lumen of the pylorus measured only 2 mm. in diameter, with no hypertrophy of the walls. This man suffered from his infancy from nausea, bloatedness, and other dyspeptic symptoms. The stenosis in this case was apparently congenital; nevertheless, the owner of this exquisitely narrow pylorus managed to attain the age of forty-five years.

Turning to our case again, it would seem to me that the life-history of this stomach could properly be divided into three phases: first, the phase of simple insufficiency, then the phase of attempted compensation, and, finally, the phase of atony and permanent gastro-ectasia. The stomach of this new-born, when filled for the first time to its full capacity at the first feeding, could, in the interval before the second feeding, empty only a part of its contents through the stenotic pylorus into the intestines. When the second feeding took place there was still present in the stomach a balance of the previous food; the organ then became over-distended. But the increased distention of the muscular walls called forth, as usual, an increased contractility of its normal muscle-fibres, and herewith a greater pressure of the walls of the stomach was exercised upon the contents, which were now driven out into the intestines in a somewhat greater proportion than in the former interval. Notwithstanding this greater removal, the balance too remaining in the stomach was greater now than in the foregoing interval. After a few feedings when, through the accumulation of the several balances, the stomach became extremely distended and

the muscular fibres were incensed to their utmost contraction, the high pressure which was now exerted upon the contents of the stomach became capable of overcoming the tonic contraction of the cardia, and the entire contents, or most of them, were now expelled through the œsophagus. After this forcible evacuation the normal stomach probably assumed its original dimensions, and the circle could commence anew. The temporary distention of the stomach is not yet gastro-ectasia, the stomach walls yet retained their full tonus, but there already existed a state of insufficiency—the stomach was unable to sufficiently empty its contents into the intestines. The body is under these circumstances insufficiently nourished, and though, with the increased pressure within the stomach, a greater transmission of food into the intestines takes place, the amount is probably incongruent with the requirements of a body in its first growth. Herein lies the cause for the greediness which the child displayed in taking the nursing bottle; and as for the constant crying of the child, there are still several other reasons. The over-loaded stomach undoubtedly gives a sense of uneasiness, then the increased contractions of the stomach might cause some pain, and perhaps, also, the contractions of the hypertrophic pylorus cause special pain, and especially when there is a struggle between the antagonistic contractions of the stomach and of the pylorus. In adults, we know that in stenosis of the pylorus the cardialgic pain is a predominant symptom. Greediness and restlessness have been present from the very beginning in many of the reported cases of congenital stenosis of the pylorus.

The constant over-distention of the stomach causes, after a longer or shorter period, a more or less pronounced degree of hypertrophy of the muscular sheath of the stomach. When this is accomplished it then has the effect of responding even to a moderate over-distention with an inadequate strong contraction capable of throwing out the entire contents through the cardiac aperture, and this the more so when, after repeated attacks, the aperture becomes somewhat dilated. It is my belief that the appearance on the scene of the frequent attacks of vomiting immediately after drinking, without other catarrhal symptoms, is a sign that a compensatory hypertrophy of the muscular tissue of the stomach had already taken place. In one of the cases recorded by Hirschsprung the author hardly credits the statement of the parent that the child appeared to be perfectly well in the first ten

days of its life. This, however, is apparently rather the rule. In most of the cases on record the frequent vomiting did not set in immediately after birth, but one or more weeks later, which finds its explanation, as I believe, in the assumption made above, that the frequent vomiting started with the development of the compensating hypertrophy of the stomach, which, of course, does not set in until some time after birth.

The pressure which the contraction of the hypertrophic muscular walls exerts upon the contents of the stomach affects not only the cardiac apertures but also the aperture of the pylorus and the conditions of the fundus. In the former case the effect might be a favorable one, the increased pressure might help to dilate the stenosis just as it overcomes the tonic contraction of the cardia. Its effect upon the fundus, however, is decidedly an unfavorable one. The walls of this part of the stomach are less muscular and do not take part in the hypertrophy of the rest of the organ. When now the hypertrophic pyloric portion exerts a considerable pressure upon the contents it drives a part of them into the resistless fundus with the result that this part becomes gradually more and more dilated. The evacuating power of the pyloric portion does then not empty all the contents, but rather a considerable portion remains in the fundus; this remaining portion of the contents becomes larger and larger, the larger the fundus is. Finally, the contraction of the hypertrophic portion becomes ineffective, or, what is still worse, this portion itself loses its contractility, the muscle fibres become degenerated through over-exertion, assisted perhaps by the malnutrition, and then the final state of gastro-ectasia is reached.

Diagnosis. The diagnosis of the last stage of the permanent gastro-ectasia offers no difficulty. The mere inspection reveals the contrast between the bulging of the upper part and the collapsed state of the lower part. Then the percussion of the stomach filled up with air or water; the palpation of the catheter within it, and the auscultation of the gargling sound produced by the air blown into the partly filled stomach, as described above, will sufficiently demonstrate the presence of a gastro-ectasia. In the second stage we might rely upon the following symptoms: The change of the area of percussion with the degree of filling of the stomach, the appearance of peristaltic waves over the region of the stomach, the palpation of the contracted

stomach in an empty stage. In both these stages, but especially in the stage of the compensatory hypertrophy, the frequent vomiting immediately after drinking, the absence of vomiting at any other time, the absence of bile from the vomit, and its non-catarrhal appearance, are quite characteristic symptoms for stenosis of the pylorus.

In the first stage we will rarely be consulted, but if we see a child which is extremely restless and drinks greedily we ought to think of the possibility of a congenital stenosis of the pylorus, and our next step ought to be to introduce a catheter, two hours after feeding, into the stomach and empty it. If we then find in the stomach a noteworthy balance while the amount of the feeding was normal, we know that there is an insufficiency present, and have to watch the further development. The introduction of a catheter for the sake of establishing the sufficiency or insufficiency ought to be done in all the stages of this disease and in all cases where we find frequent vomiting.

TREATMENT. In treating this affection we have to remember that there are cases on record where the patients managed to live to a comparatively high age with a very narrow pylorus. But we should also remember that a piece of tenacious mucus, a large coagulum sticking in the pylorus, or a slight kink of it, would suffice to make such a pylorus entirely impenetrable. We must also remember that the successful passage of food through such a pylorus largely depends upon the contractility of the stomach, and that an ectatic stomach does not contract, and, moreover, is liable to produce by its weight fatal kinks of the pylorus. The treatment of the first and the second stages consists mainly in two points: the proper regulation of the feeding and the frequent emptying and washing of the stomach. With regard to feeding, it would seem to me that at least in the first stage the amount given at one time should slightly overstep the capacity of the stomach. The distention which is caused by it will bring out a better contraction of the muscular tissue, which will not only drive more food into the intestines, but might also serve to a degree as a means of gradual dilatation of the stenotic pylorus. The emptying of the stomach, however, must be done quite frequently; the washing is, under these circumstances, a less important matter, and the emptying alone is such an easy procedure that it could be carried out after some practice by any member of the family. In the second stage only a small amount can be given, as larger ones would immediately

be rejected by the stomach; but the feeding must be carried on very often, at least hourly. In the early period of this stage it is probably sufficient to empty and wash the stomach once a day, as the frequent vomiting partly acts as a safety-valve against the overcrowding of the stomach. It should not be attempted to stop the vomiting by means of narcotics or bismuth. I have used a narcotic myself, and I see in Finkelstein's statement that Heubner also used it. However, I now think that they are harmful, inasmuch as they paralyze the contractility of the stomach, which is the most indispensable factor in our struggle. Bismuth might entirely obliterate the small opening of the pylorus. For the same reason I believe that cow's milk should not be employed in these cases, as it forms large coagula in the stomach. Heubner's method of washing the stomach with ½ per cent. of Carlsbad salts should be employed. It will help to keep the narrow passage of the pylorus free from mucus. The tenacious mucus which was found in my case to stick within the pylorus might have been the cause of the absolute occlusion which was observed in the two days previous to the operation. Massage of the stomach in the direction from left to right should be practised, which might assist the stomach in emptying its contents into the intestines. A bandage around the stomach might also prove to be beneficial, but it ought to have a pad fitting and filling out the epigastrium and reaching to the navel, in order to exert an efficient pressure upon the stomach, which might prevent to a degree its extreme dilatation and help it at the same time in pressing its contents into the intestines.

That the rectum should be utilized for additional nutrition, and that hydropathic and other measures to improve the general condition of the little patient should be employed is self-understood, and does not require any particular discussion.

In the last two stages, besides all the measures mentioned above, there comes in addition the operative treatment into consideration. In adults the operative treatment for benign strictures of the pylorus is an established procedure, and, as it is well known, furnishes quite favorable results. For the class of cases we are dealing with here, Schwyzer was the first one to discuss the advisability of surgical interference. He mentions Loretta's operation and gastro-enterostomy. Loretta's operation, or the digital divulsion of the pylorus, is appar-

ently here out of the question, especially where the lumen of the pylorus measures not even 1 mm. in diameter. Gastro-enterostomy, however, is at present generally employed in cases of benign strictures of the pylorus in adults, and is, naturally enough, the operation which suggests itself for the relief from the hypertrophic stenosis of the pylorus in infants. And here, again, where the gain of time is surely a very important point, apparently Murphy's button deserves the preference over the anastomosis by suture. The operation in my case, the first one ever performed for the relief of congenital stenosis of the pylorus in infants, was done with the Murphy button, and was not a success; this, however, was only due to the inadequate size of the button, which can be avoided in the future. Indeed, Dr. W. Meyer has now had small buttons made which will probably not block the free passage in the jejunum of even very small infants, and he is of the opinion that the button ought to be given the preference over the anastomosis by the suture, in fact, over any other method.* It seems to me, however, that there are well-founded objections to the employment of a Murphy button in infants. In the first place, it is very probable that here the button will not pass off through the very narrow, exceedingly contracted jejunum, but preferably enter into the stomach to remain there. In the second place, there comes up quite a serious question as to the future effectiveness of the small communication established by the small button between the stomach and the intestines. In a case of Czerny, where the opening made at the operation measured 3 cm., it was found at the autopsy, five months later, that the opening was reduced to only 8 mm. This occurred in an adult in whom the solid food taken by the patient might yet have a dilating tendency upon the opening. What, then, will be the fate of the opening in the stomach of an infant with its liquid food? And it would seem to me that the growth of the stomach and the body in general would rather exercise an obliterating tendency upon the artificial opening. We must also bear in mind that the motility of the stomach is arranged to propel the food in the direction toward the pylorus and not toward the places usually selected for the artificial opening, and that the peristaltic wave, instead of assisting in pressing

* Soon after the operation in my case, Dr. I. Adler, in New York, met with a similar case, and here Dr. W. Meyer made the gastro-entero-anastomosis by suture. This child, too, died a short time after the operation. But the baby was, as I understand, in a very debilitated state.

the food through the artificial opening, will rapidly carry it away from there. These considerations, however, speak not only against the use of the Murphy button, but also make the advisability of the employment of gastro-enterostomy in infants altogether questionable.

It seems to me, therefore, that the typical pylorectomy (Billroth) is the ideal operation for the relief of the hypertrophic stenosis of the pylorus in infants. The objections against the use of this operation in the stenosis of the pylorus in adults arose mostly from its exclusive employment in malignant cases, where the adhesions, etc., made it quite a difficult operation It seems that even there we are now on a turning-point in its favor. (See Keen in *Cartwright Lectures.*) In cases of benign stenosis in infants the removal of the hypertrophic pylorus will re-establish normal conditions, provided the stomach did not lose its efficient motility. And here I would like to emphasize very strongly that any operation will hardly be a success if it is done when the state of gastro-ectasia has already been permanently established. There will be at this time quite a progressive state of marasmus, and the child will not stand any operation. The indication for the operation is already given in the second stage, when the empty stomach starts to show some degree of dilatation. And even without any dilatation if, after evacuating and washing the stomach for many days, the child still continues either to vomit immediately after drinking or to retain a large part of the food for hours, while gaining very little in weight, then there is a proper indication for the operation. We must also bear in mind that such infants, even if we succeed in assisting them to overbridge the dangers of their early life, will in all probability be invalids all their life long; there will always be a misproportion between the stomach and pylorus, a gastric insufficiency, with all its consequences upon body and mind! We should, therefore, not hesitate to operate, and should operate early, the operation should be performed while *the stomach yet shows distinct and strong peristaltic movements.* When the operation is done early the child will survive it; and when the hypertrophic pylorus is removed while the hypertrophic pyloric portion of the stomach is still capable of efficient activity, the motile function of the stomach will be restored in an ideal way.

There are at present on record 22 cases of congenital hypertrophic stenosis of the pylorus in infants, in which the diagnosis was estab-

lished or verified by autopsies. They are as follows: Williamson,[7] 1841, 1; Davoski,[8] 1842, 1; Hirschsprung,[9] 1883, 2; Peden,[14] 1889, 1; Henschel,[4] 1891, 2; Pitt,[15] 1892, 1; Finkelstein,[2] 1896, 1; Gran,[10] 1896, 3; De Bruin Kops,[16] 1891, 1; Thomson,[17] 1896, 2, and 1897 1; Schwyzer,[18] 1896, 1, and 1897 1; Soltau Fenwick,[19] 1897, 1; Ashby,[1] 1897, 2; Rolleston and Hayne, 1898, 1; Finkelstein includes a case of atresia of the pylorus by Loesschaft;[20] the atresia in this case, however, was within the duodenum, about 6 mm. away from the pyloric valve. The degree of the stenosis given in these cases shows a considerable variety between the passability of a "fine probe," a "middle-sized probe," or even the "little finger."

R. Maier divides the cases of congenital stenosis of the pylorus observed by Landerer and by himself in adults in simple and complicated stenosis according to the absence or presence of a hypertrophy of the pylorus, and states that in their 31 cases 8 were of the uncomplicated variety. It is a noteworthy fact that *in the* 22 *cases of congenital stenosis of the pylorus in infants there is among them not one of the simple variety; all were more or less distinctly complicated by hypertrophy.* This would seem to permit the interpretation that it is the rigid hypertrophy which makes the stenosis a fatal anomaly, while a simple congenital narrowness of the pylorus is distensible enough to be overcome by the natural or acquired forces of the stomach, and it is therefore not fatal. We can thus understand how an individual with a pylorus of only 2 mm. in diameter (first case of Landerer) could attain an age of forty-five years. As to the hypertrophy in the complicated cases of Maier and Landerer, there is nothing in the way of assuming that it was not congenital, but acquired in the struggle of many years.

In this connection it deserves to be further pointed out that in many of the cases of the hypertrophic stenosis in infants it is distinctly stated that longitudinal folds were present in the narrow lumen of the pylorus, which would seem to indicate that without the constricting effect of the surrounding hypertrophic tissue the mucous membrane alone would present a lumen larger than the actual diameter, though probably still narrower than in a normal pylorus.

As to the nature of the hypertrophy, the first writers on this subject, Williamson as well as Davoski, have described the conditions they found as hypertrophy of the submucous tissue. But this happened at

such an early period in the microscopic era that we might yet, with Thomson, believe "that it was the muscular layer really which was affected." In our own case, however, according to the description of Dr. Prudden, the fibrous hyperplasia of the submucosa has a prominent share in the production of the thickening of the pyloric wall. Other writers, too, expressly report that all the layers of the wall evenly shared in the hypertrophy, for instance, Hirschsprung's first case, and Thomson himself reports in his third case "that here submucous connective-tissue was greatly increased in amount." It seems to me, therefore, that Thomson goes too far when he asserts "that the whole narrowing of the passage seemed to be due to compression by the hypertrophied muscle," or "that in all the cases . . . . the thickening of the pylorus was due mainly to great hypertrophy of the circular layer of muscular fibres." With regard to the participation of the muscle-fibres in the hypertrophy, R. Maier divides the cases of complicated stenosis observed by Landerer and by himself into two forms. In the first form the duodenal end of the pylorus terminated in the shape of the vaginal portion of the uterus, while the gastric end appears to be funnel-shaped; in this form, Maier says the hypertrophy is made up by the longitudinal muscle-fibres. In the second form the pylorus appears to be like an intermediate piece (Zwischenstueck) between the stomach and duodenum, and consists of a hyperplasia of the circular muscular fibres of the pyloric valve. The description of most of the cases of the hypertrophic stenosis in infants seems to fit the first form of Maier: there is the funnel-shape in one end and the shape of the vaginal portion at the other end of the pylorus; nevertheless, there is quite a general agreement among most of the writers that the hypertrophy is made up by the circular fibres. This seems to be the rule, to which there are, so far, only two exceptions—the case of Finkelstein and the second case of Hirschsprung. There is apparently room enough left for a further study of the anatomy of our cases.

As to the etiology of these cases there is at present only the one hypothesis, which was put forward by Thomson and found favor with some of the subsequent writers. Thomson's theory is as follows: The primary lesion is "a functional disorder of the nerves of the stomach and pylorus, leading to ill-coördinated, and, therefore, antagonistic action of their muscular arrangement." The fault in the

nervous mechanism "is probably due, in some way, to delayed or imperfect development." "The antagonistic spasm of the pylorus and stomach must be connected with the passage downward of the large quantity of liquor amnii which the fœtus is believed to swallow during the later months of intra-uterine life." "The muscular hypertrophy of the walls of the pylorus and stomach is merely a secondary occurrence, being obviously due to abnormally increased activity, and this must have existed for a considerable period of the intra-uterine life."*

This theory, I must confess, does not appear to me as a very probable one. It is apparently based upon the presupposition that the hypertrophy is confined to the muscular fibres, and that muscular hypertrophy can be due only to some sort of over-action. We have, however, already demonstrated above that in many of the cases the submucosa had a prominent share in the formation of the hypertrophy, and that in all the cases there was some degree of hyperplasia of the submucous tissue. A disorder of the nervous mechanism would not account for the hypertrophy of the connective tissues. Moreover, the assumption that a tonic contraction of the pylorus would lead to a hypertrophy of its own muscular coat seems to me to be without any foundation. A stricture of any kind leads to a muscular hypertrophy of the parts lying in front of it, but does not cause a muscular hypertrophy in the stenotic region itself. Pyloro-spasm in adults does not lead to hypertrophy of the pylorus, and cardio-spasm does not lead to muscular thickening of the cardia. Cicatricial stenosis in any of the muscular tubes of the body does not lead to muscular hypertrophy within the stricture. And even of the cases of congenital hydronephrosis, with greatly hypertrophied bladder, which are quoted by Thomson as a parallel to our cases, the author himself says that "no organic obstruction exists to the passage of urine." A spasm of the constrictor vesicæ might lead to the hypertrophy of the detrusor but not to that of the constrictor itself. Furthermore, admitting even that the over-action of the pylorus could lead to its thickening—how should the over-action cause a considerable elongation of the pylorus, which is observed in nearly all the cases? The thickening of the walls of the pyloric portion of the stomach is generally admitted to be an acquired condition, which, by the way, was not present in some

* Thomson was so sure of the correctness of his theory that he termed the condition "congenital gastric spasm." It is, however, always safer to derive a title rather from sure facts than from theories which are mostly disputable.

of the cases. It seems to me that by accepting the congenital muscular hypertrophy of the pylorus, not as a secondary occurrence, due to some over-action, but as a primary lesion, simply as an embryological malformation, we make a much less risky hypothesis than that made by Thomson, which establishes, without safe precedent, an embryological disorder in the nervous mechanism of the pylorus, of which we know so little in the fully outgrown animal. And, after all, it is not simply a hypertrophy of the muscular tissue; it is the hypertrophy of all the tissues of the pyloric valve; it is, so to say, the hypertrophy of an organ. The pyloric valve has variable dimensions in different individuals, and it might occur that in one or the other individual it attains such a size as to be pathological in a teleological sense. The structure of the hypertrophic pylorus reminds one very much of the normal structure of the ileo-cæcal valve, in which, too, the longitudinal muscularis does not participate in the formation of the fold. In this connection it is worthy of mention that Brandt[21] described a case in which there was a hypertrophic stenosis of the pylorus as well as of the ileo-cæcal valve.

LITERATURE.

1. Ashby, H. Archives of Pediatrics, 1897.
2. Finkelstein. Jahrbuch fuer Kinderheilkunde, 1896, vol. xliii. p. 105.
3. Thomson. "On Congenital Gastric Spasm," Scottish Medical and Surgical Journal, 1897.
4. Henschel. Archiv fuer Kinderheilkunde, 1891, vol. xiii. p. 32, x.
5. Schwyzer. New York Medical Journal, 1897.
6. Rolleston and Hayne. British Medical Journal, April 13, 1898, p. 1070.
7. Williamson. London and Edinburgh Monthly Journal of Medical Science, 1841, p. 23.
8. Davoski. Caspari's Wochenschrift, 1842, No. 7.
9. Hirschsprung. Jahrbuch fuer Kinderheilkunde, 1888, vol. xxiii. p. 61.
10. Gran. Jahrbuch fuer Kinderheilkunde, 1896, vol. xliii. p. 118.
11. Landerer. Ueber angeborene Stenose des Pylorus, Dissertation. Tuebingen, 1879.
12. Rud. Maier. Virchow's Archiv, 1885, vol. cii. p. 413.
13. Heubner, quoted by Finkelstein.
14. Peden. Glasgow Medical Journal, 1889, p. 416.
15. Pitt. Transactions of Pathological Society, London, 1892, p. 63.
16. De Bruin Kops. Nederlandsch Tijdschrift voor Geneeskunde, 1896, No. 19 (after Thomson).
17. Thomson. Edinburgh Hospital Reports, 1896, vol. iv. p. 116.
18. Schwyzer. New York Medical Journal, Nov. 21, 1896.
19. Fenwick. The Disorders of Digestion in Infancy and Childhood, London, 1897.
20. Loesschaft. Jahrbuch fuer Kinderheilkunde, vol. xxii. p. 164.
21. Brandt. Die Stenose des Pylorus, Dissertation, Jena, 1851.

DISCUSSION.

DR. I. ADLER: It may be of interest, perhaps, to show another specimen of a case almost identical with the one reported just now, for these cases are

still comparatively rare. I do not wish to take up time by going into detail. Let me merely say, very briefly, that this specimen was taken from a child eleven weeks old, which at birth was perfectly normal, which fed normally, and only after the second week or so commenced vomiting. The vomiting persisted, without any signs of sickness, and the child had a ravenous appetite. The diagnosis was established on the fact that the vomiting was of a peculiar character, the stomach was dilated, and its peristaltic movements could be called forth at any time on touching the abdomen. At first it was attempted to feed the baby and avoid an operation until it became older, but the child lost weight, became miserable, and the operarion had to be resorted to. Profiting by Dr. Meltzer's experience, Dr. Meyer, who operated for me also, had a small Murphy button made, but we found it better to make a gastro-enterostomy by suture. The operation lasted somewhat long, on account of the difficulty in putting back the liver and intestines that had protruded. The child died twelve hours after operation, of shock. The diagnosis was confirmed at autopsy. There was no inflammation of any kind, and the child had simply died of shock from the operation.

I should say that a microscopical examination of the specimens, though not yet completed, showed a hyperplasia principally of the circular fibres, the longitudinal fibres being but little altered.

DR. A. JACOBI: These cases appear to multiply. In last week's London *Lancet* there is a case of the same kind reported by Rolleston and Hayne. Another case has not been mentioned in the literature that I have seen in the last report of Monti. It was published by De Bruin Kops in the *Netherland Obstetrical Journal* of 1896. The baby died a few weeks after birth. The stomach was large and horizontal. The pylorus was hard, the tumor-like hypertrophy as large as a marble, and consisted of muscular tissue.

Nobody was aware a short time ago that such cases existed, but now they are multiplying to a great extent.

There is one thing I would like to know. Dr. John Thomson, of Edinburgh, who has published three cases, considers them as due to "congenital gastric spasm." I think embryologists ought to take hold of the cases and study their origin. I have not been able to believe that spasm is the original cause. Dr. Thomson believes that there is a simultaneous spasm of the pylorus and stomach, brought about by nervous inco-ordination. There is nothing which should act as an irritant during fœtal life. The liquor amnii is certainly not irritating, and the hyperæmia of the mucous membrane which was found in some post-mortem examinations was probably an effect, and not a cause.

DR. MELTZER: In regard to Thomson's theory, it seems to me rather strange to assume that the hypertrophy of the pylorus should be due to its own tonic contraction. We know that hypertrophy occurs in front of a stricture, but we do not know of any instance where a constant tonus will produce hypertrophy of the muscle-tissue lying within the contracted region.

THE TREATMENT OF CHRONIC INTERSTITIAL NEPHRITIS.

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As our knowledge of the natural history of chronic interstitial nephritis has increased our methods of treatment have naturally and progressively improved. It is my purpose in the present paper to describe briefly my own mode of treating this disease and of relieving the perplexing complications which arise during its course.

It is obvious, however, that no general rules can be laid down which are applicable to every case. But there are certain principles which must govern the physician's tactics, which seem to be fixed and settled, and which must certainly be regarded as having the force of law until and unless our ideas of the pathology of interstitial nephritis shall undergo a radical change.

These are: (*a*) Abstinence from alcoholic beverages of all kinds. (*b*) The selection of a dietary which throws the least possible strain upon the organs chiefly concerned in retrograde metamorphosis; in other words, the dietary most directly and easily respondent to combustion or oxidation. (*c*) The continuous and persistent employment of tonic and alterative remedies or remedies which have hæmogenetic power, along with remedies which have alterative or metabolic power.

(*a*) The first of these propositions needs neither demonstration nor argument. It has already passed into an axiom. Every experienced clinician knows only too well how frequently alcoholic beverages are justly charged with exciting interstitial nephritis. And this is especially true of those patients who are "moderate" but habitual drinkers; whose kidneys are constantly engaged in eliminating alcohol, and are, therefore, constantly suffering alcoholic irritation. The dangers to the kidney are far greater in moderate but habitual drinkers

than in those who go on periodical "sprees," followed by seasons of total abstinence and a gush of temperance oratory. After the kidney has once entered upon the changes which constitute cirrhosis it is doubly sensitive to alcoholic irritation. It should, therefore, be an inflexible rule that all alcoholic beverages be dropped entirely and permanently. It is also important that those noxious and filthy compounds, such as "root beer," "birch beer," "ginger ale," and the whole category of so-called "temperance drinks" which are now so commonly found in the homes of the most exemplary people, should be rigidly excluded from the list of beverages of patients having contracted kidneys.

(*b*) The question of diet in cases of interstitial nephritis is still a *questio vexata,* and is likely to remain so until we have more successfully explored the hazy field of gastro-hepatico-intestinal dynamics. But it seems to be unquestionable that a highly nitrogenous diet is positively injurious in all renal lesions, and the reason for this result seems definitely settled—namely, the fact that a nitrogenous diet is uniformly followed by the accumulation of lithic acid in the blood and tissues, and the consequent phenomena characteristic of "lithæmia." In clinical experience we commonly find that cirrhosis of the kidneys is accompanied by some degree of hepatic cirrhosis, and that the functional capacity of the liver suffers accordingly. It seems to be a well-settled postulate of physiology that the liver, more than any other organ, is concerned in converting insoluble uric acid into soluble urea. The healthy kidney readily seizes upon and eliminates urea; the contracting kidney surrenders this power reluctantly and slowly; the healthy kidney cannot eliminate uric acid with comfort and facility, and its presence is always unwelcome to the renal cells, while the contracting kidney is seriously irritated and injured by its presence. It is, therefore, of great practical importance that the dietary be selected with the view of reducing the output of uric acid to the minimum. And this question must be settled by the practitioner—not according to arbitrary rules, even though they seem to be sanctioned by physiological laws and clinched by that delusive phantom called "experience," but by the results attained in each individual case. One patient can be confined pretty closely to a diet of milk and fruits, without suffering gastric torments and an aggravation of renal symptoms; he can oxidize milk freely

and rapidly; hence, milk is the ideal diet for him so long and *only* so long as these conditions remain. The very next patient may revolt at a milk-diet; it may cause gastro-intestinal mutiny, and if so, it is all but sure to be followed by increased albuminuria, uric acid, and casts, and the nervous phenomena of lithæmia. But he can take a meat- and vegetable-diet with both comfort as regards digestion and profit as regards the renal indications. Plainly, a nitrogenous diet is the proper regimen for him, in spite of the fact that he is committing physiological heterodoxy. But a question of very great practical importance is, How shall the physician decide what is the proper diet in the individual case? The answer is not by any means difficult. It is obtained chiefly through the agency of the test-tube and the ureameter. A decreasing ratio of urea and increasing percentage of albumin, together with the coincident presence of the symptoms of uric acid toxæmia, should determine a change of diet, whatever it may be. This rule is a much safer one than any arbitrary dictum based upon observations in cases other than the one in hand. At the bedside in private practice, and especially in hospital practice, we are too apt to forget that every patient has his own peculiar digestive apparatus, which will manifest its own individuality in contempt of the most highly scientific deductions or the most carefully prepared diet-list. Another practical point must not be forgotten: change of diet—variety—is quite as essential to the renal invalid as to a healthy person. When it was written "man shall not live by bread alone," the term "bread" was used in a generic sense, and included milk and meat as well. When the patient wearies of his prescribed diet, the digestion fails and assimilation becomes faulty; then elimination is interrupted and auto-intoxication follows as an inevitable result. It does not matter so much what the particular form of diet is in interstitial nephritis, provided it be acceptable to the digestive apparatus of the patient to whom it is given; provided the quantity be not too great for the actual demands of the patient, so that there shall remain an unused overplus to be converted into lithic acid or its congeners by imperfect combustion.

The question of diet for a renal invalid is one of individual nature, not to be settled by an appeal to laws—physical, pathological, or chemical—but rather by the findings of the test-tube and the ureameter, corrected and verified by the complex of coincident symptoms

While it is true that milk is an ideal diet in renal diseases, it is also true that every now and then we stumble upon a patient with contracting kidneys who does best upon a flesh-diet, in spite of all our rules. I am accustomed to allowing fruits of all kinds; in fact, I advise their free and habitual use. The fruit-acids do not disturb digestion, while they do gently stimulate and encourage the faltering liver and kidneys.

It is also very essential that patients with interstitial nephritis be encouraged—in fact, be required—to drink freely of pure water. It is just on this point that I experience my greatest difficulty. It is almost impossible to get patients to ingest habitually a proper amount of water. They will manfully swallow drugs *ad nauseam*, but they revolt at the idea of drinking four or five glasses of pure water a day. Hence, because I deem it very essential that the kidneys be "flushed" with water daily, I am obliged to resort to various harmless "remedies," to be dissolved in a full glass of water and taken on an empty stomach four or five times a day, for the purpose of accomplishing the object in view.

The waters of the various "lithium" springs serve a good purpose in this regard, since they at least possess the negative virtue of containing nothing harmful.

(*c*) Have medicines, *per se*, any value in interstitial nephritis? Answering this question for myself, I have to say, first, that no remedies within my present knowledge will radically cure interstitial nephritis; in other words, the damage once done can never be removed or repaired by any means within our present reach; secondly, a proper treatment, persistently pursued, in an uncomplicated case will frequently arrest the progress of the cirrhotic process and prolong the patient's life even to the allotted age of man.

According to my way of thinking, there are three objects to be kept in view in addressing treatment to a case of interstitial nephritis:

(*a*) The persistent use of alterative remedies.

(*b*) The use of hæmogenetics or tonics when they are clearly indicated.

(*c*) The care of the heart.

(*a*) The alterative remedies to which I attach most value are mercury and iodine, with a growing tendency in favor of gold also. Up to the present time, however, my preference is for mercury, persist-

ently administered in minute doses three or four times a day. Of the mercuric salts, calomel, in doses of a tenth to a quarter of a grain three or four times a day, is my first choice. My intention is to so graduate the doses as to exert a barely perceptible effect upon the bowels, and generally the smaller dose mentioned will be sufficient. It should be administered persistently, not less than three times a day, and four times a day is better, for periods of six weeks to three months. It will, on rare occasions, produce tenderness of the gums, which I never regret; but I have never had ptyalism follow its use in the manner indicated.

Of course, the patient and the dose must be studiously adapted to each other.

The mercuric protiodide is scarcely less valuable, although its effect on the alimentary tract is less certain and pronounced. As an "alterative" to the hyperplastic connective tissue of the kidney, its value is, in my judgment, undeniable.

Mercuric bichloride and mercuric biniodide are probably quite as valuable as the milder salts recommended; but I have not used them much, preferring to employ remedies with which I am more thoroughly acquainted rather than those which are comparative strangers.

Iodine uncombined, as in Lugol's solution, is a most valuable remedy when it is tolerated. Many patients cannot bear it at all, as it causes gastric irritation and general disturbance of the assimilating and eliminating organs. In clinical experience, therefore, it is generally necessary to seek the effect of iodine through the agency of its "haloid" combinations. Gold, as a slowly-acting but quite certain alterative or resolvent of morbid connective-tissue growth, is assuredly growing in favor among those best acquainted with its properties. Its effects seem to be quite like those of iodine, except that its action is less rapid—*not*, however, less sure. The chief objection to gold is that its compounds are not sufficiently permanent or stable for general use. The chloride of gold and sodium—the most eligible preparation—may be employed in gelatin-coated pills, which should be kept tightly corked and in the dark.

There are certain proprietary preparations of gold on the market, concerning which extravagant claims are made, but they are no more efficient than the preparation just named.

I have certainly seen valuable results from the prolonged use of gold in renal cirrhosis.

(*b*) In nearly every case of chronic interstitial nephritis the demand for hæmogenetic agents arises sooner or later. But while anæmia is a pretty certain consequence of this disease, it varies greatly as to the time of its appearance in different cases. It is not due to loss of albumin so much as to loss of assimilative power. Hence, it does not follow that a patient needs tonics simply because he has renal cirrhosis, and, hence, as I have already said, they should be administered "only when they are clearly indicated." It should also be remembered that when the patient cannot assimilate food, neither can he assimilate iron or other hæmogenetics.

Iron still remains the ideal tonic in the anæmia of interstitial nephritis, having maintained its supremacy against all other remedies up to the present time. So numerous and so well known are its preparations that very little need be said about it. My personal preference is for the ferric citrate, because it seems to me to produce less gastric irritation, or rather gastric irritation in a smaller number of patients, than any other chalybeate. If a diuretic happens also to be needed, potassic citrate may be combined with the ferric citrate, as in the following formula, which I have employed times without number:

℞.—Ferri citratis	. . . . .	160 grains.
Potassii citratis	. . . . .	320 "
Syrupi limonis	. . . . .	2 ounces.
Aquæ, q. s. ad	. . . . .	8 "

Sig.—Take a dessertspoonful before each meal, well diluted.

Concerning such preparations as "hæmoferum" and similar vaunted bloodmakers I have no practical knowledge.

Of late I have been impressed with the value of manganese as a hæmogenetic and also as an oxidizing agent, which is much needed in renal inadequacy. I have seen much improvement follow its use, not only in the general appearance of the patient but also in the steady increase of red blood-globules, as proven by comparative counts. I have generally employed the binoxide in doses of three grains three times a day. I have also employed the proprietary preparation known as "Liquor Pepto-mangan" with good results, in

spite of my aversion for the whole brood of proprietary remedies, with their *bizarre* names.

Diuretics are *not* indicated *because* a patient has interstitial nephritis, although they may be occasionally required, just as cholagogues are now and then required during the treatment of interstitial hepatitis. In neither instance do they "cure" or essentially modify the disease, except that they irritate and worry the diseased organ when used injudiciously.

When diuretics are indicated by scantiness of urine, or a very low percentage of urea, or much deposit of waste material from the kidneys, showing that the renal tubules are filled and clogged by products of degeneration, or by the appearance of symptoms of uræmic toxæmia, they must be given, of course. The saline diuretics are always preferable; potassic citrate, sodic acetate, potassic acetate, potassic bitartrate are, in my estimation, valuable in about the order named. They ought always to be given when the stomach is empty, and largely diluted, but they ought to be suspended when they are no longer clearly indicated.

(*c*) Lastly, the care of the heart must engage the serious attention of the physician. This branch of the subject is of sufficient importance to demand separate and detailed treatment. At present I can only give a few brief hints of a very practical nature.

In the early stage of interstitial nephritis, when progressive hypertrophy of the heart, and especially the left ventricle, is going on, when the powerful and angry contractions of the thickened ventricle provoke resistive spasms in the far-off but already thickened arterioles of the kidney, so that there exist between these two a condition of mutual contention or defiance, the heart itself needs no medication. It is generally sufficient to diminish the alloxuric bodies to the minimum by eliminative remedies and a few days of strict antinitrogenous diet. If, however, the heart contractions become a troublesome palpitation, the patient should be placed in a recumbent position for a few days, and a little aconite or some equivalent remedy should be given just long enough, but *only* long enough, to calm and equalize the tumultuous action of the organ. At this stage digitalis and other cardiac tonics ought to be avoided for reasons too obvious to require argument. At a later period, when the heart, yielding to the inevitable, exhausted by the long but unequal contest with the thickened,

inelastic, and tortuous renal vessels, becomes dilated and thin-walled, it will be necessary to resort to heart-tonics, whereof the most valuable is strychnine; the next in order is ergot, and then comes a group of remedies, headed by digitalis and supplemented by strophanthus, convallaria, and adonis vernalis. In each and every case the conservation of the heart must be committed to the judgment of the medical attendant, and well it is for the patient if the medical attendant be a man of judgment tempered and corrected by experience.

Of course, it will be understood that the foregoing remarks are in the main applicable to interstitial nephritis in the early and advancing stage only.

SOME USUALLY OVERLOOKED PHYSICAL SIGNS AND SYMPTOMS IN CHEST DISEASES.

By NORMAN BRIDGE, M.D.,
OF CHICAGO AND LOS ANGELES.

THE tendency of the mind of the young doctor, and sometimes of the older one, is to look for the classical and typical changes in all chest diseases. He knows well what ideal bronchial breathing is; what râles are, and the different sorts; what pectoriloquy, egophony, amphoric sounds, and metallic tinkling mean. He knows flatness on percussion and dulness when marked, and cracked-pot percussion sound with open-mouth breathing. And if these, or a combination of them, are found in any case, diagnosis is supposed to be thereby relatively easy.

In our early studies we learn to look for these signs, and are disappointed sometimes when the symptoms have led us to expect to find them and we do not find them. Failing to discover them, we sometimes wholly fail to detect other ample physical signs, that are, however, less prominent and pronounced. The descriptions in the text-books have given us these and similar classical signs as they are found in their perfection, and we are liable to dwell on them so fully that anything short of their ideal manifestation we pass over and hardly notice. This is one of the faults of our usual method of study, which is to consider the sick from the stand-point of the classical description of the different diseases, and try to find the right picture to fit each case, rather than from the clinical stand-point of the symptoms and signs which the patients, as they come to us, actually have.

Now, in certain lung diseases—notably, tuberculosis—it is of the greatest possible moment to be able to make an early diagnosis. Many a patient, who must otherwise die, could be helped if the diagnosis were made early and before the different or any of the classical physical

signs are completely developed. To do this we must invoke several aids and tests not usually thought of. We must learn to detect slight changes from the normal conditions, the first intimations of those varitions of sounds in auscultation and percussion that progressively develop into classical signs. The doctor who examines his cases critically sees fortyfold more of them having these slight changes than of those which show the ideal signs. It is often not possible to secure expectoration for a search for bacilli or to make the tuberculin test.

Pulmonary tuberculosis, fortunately for this study, is usually unilateral at the beginning, and so we have early a normal side of the body for comparison. By examining the two sides critically, and comparing them with each other repeatedly, it is often possible very early to detect alterations that point unmistakably to lesions that are progressing. We perhaps find on one side a slight lessening of the force and loudness of the vesicular murmur on inspiration; or there is a slight increase in expiratory sound, at first without a particle of the quality known as tubular. Can we hear the expiratory sound better on one side than on the other? If so, there is an abnormal condition in one lung, either where the sound is louder or softer—of course, always making allowance for the slight disparity in sounds between the two apices. Later, if the change progresses, actual tubular breathing may be heard, at first with so little of the tubular quality that it can barely be perceived.

The two sides should be gone over everywhere carefully, and corresponding points of the two critically compared, to see if any anatomical region can be found where there is even a slight difference between them: In (*a*) length of the inspiratory sound; (*b*) intensity of the normal vesicular quality of that sound; (*c*) length of the expiratory sound; (*d*) intensity of this sound and the elevation of its pitch above what is normal; (*e*) vocal fremitus on the uttering of words that cause an extreme degree of vibration, as *ninety-nine*, and (*f*) the transmission to the auscultating ear of the ordinary voice and soft whisper. Râles should be searched for on deep inspiration with profound expiration, and on voluntary coughing.

Tuberculosis usually begins in a circumscribed region of one lung, and is often first seated in the bronchial mucous membrane. If there is any tendency to recovery, any conservative power, it soon causes a deposit of adventitious fibrous tissue (fibrosis) through contiguous

lung tissue, which invariably changes the physical signs and in the way indicated, only a slight change being perceptible at first, and the signs being most changed nearest the focus of disease, and shading off toward normal sounds farther away.

Finding any of these slight changes, we should carry our comparison of the two sides to other regions—all over the lungs, and find where they are most evident. That will be nearest to the focus of the tuberculosis, if this disease is present. If a deposit exists in an apex, fibrosis will spread from that point. The back is the best region for comparison of the two sides. Listening over the lower zone of the lungs posteriorly, the sounds are absolutely alike and normal on the two sides; as we rise step by step, listening over every half-inch vertically, and changing the stethoscope repeatedly from one side to the other, we soon strike a zone, perhaps at the lower angles of the scapulæ, where we can barely perceive that on one side the vesicular murmur on inspiration is a trifle less pronounced, and the expiratory sound perhaps a trifle more so, and longer, than on the opposite side at the corresponding point. One inch higher up this disparity is, while apparently not more marked, yet slightly more perceptible—which means that it must be more marked. Above this level the difference is progressively greater; the vesicular murmur is, as we ascend, growing less, and the expiratory sound greater, louder, longer, and stronger, and soon higher in pitch. Perhaps near the spine of the scapula the expiratory sound is longer than the inspiratory, and is definitely tubular, and has a pitch perhaps as high as the inspiratory sound. Over the seat of the deposit, if the bronchi are not closed by phlegm or otherwise, this tubular breathing is most striking, and is ideal if the deposit is extreme; at the same time the vesicular murmur on inspiration may be nearly gone. But if the deposit or thickening of the connective tissue is slight, the most pronounced change in the sounds does not reach an entire ablation of the vesicular murmur on inspiration, nor is there any ideal bronchial breathing, but only a slight increase in the loudness and length of the expiratory sound.

As the expiratory sound increases in loudness and rises in pitch there is always—other things being equal—a corresponding increase in the vocal fremitus over the region as well as in the transmission through the chest-walls of the voice in phonation and whisper. With patulous tubes these sounds increase in loudness, if not always in dis-

tinctness, as the solid substance of the breathing organ increases in mass.

For the interest of the patient it is in cases of just such slight alteration as here indicated that the signs are of paramount importance—that is, mainly in cases of incipient phthisis. This careful method of auscultation from side to side, and the testing of the fremitus and voice transmission, should be made in all cases where there is a particle of question as to some disease of a lung.

Many things besides tuberculosis may cause a slight disparity between the two sides of the chest, and pleuritis is one of them, and rather a common one. If the difference between the two sides is slight and uniform over the whole of both lungs at the back, and there are no other signs, then a former pleuritis is probably the cause. The disease may have occurred many years before, producing slight changes in the superficial portions of the lung, probably in the shape of permanent thickening of the connective tissue, whereby the vesicular murmur is a little reduced on inspiration and the expiratory sound is prolonged. The thickened tissue of a cured tuberculosis makes disparity of sounds between the two sides, but not a uniform one; the difference is greatest over the lesion.

In many cases of considerably advanced phthisis the physical signs are markedly reduced, especially the râles, by deep inspirations and failure to expire freely. The result of this is a distention of the bronchi and lung tissue to such a degree that the moving air does not disturb the phlegm to cause râles, and the otherwise marked bronchial breathing is nearly abolished. In a few incipient and slight cases this trick of many patients is quite enough to hide all the signs. Patients must sometimes be taught and induced to expire profoundly to enable us to detect fine râles in bronchi of only moderate size. It is an impulse of many patients to make the chest large for the doctor to listen to; it is either an act of politeness or to show themselves at their best. They first increase the lung air-contents enormously by expansion, then take in and expel but little air with each respiratory act, so that the residual air is greatly increased and the bronchi are distended, and the phlegm that lines them is not disturbed, and so no râles result. Let a full expiration be made and râles at once appear. Failure to resort to this manœuvre has, in my observation, many times caused an early diagnosis—that was perfectly

possible—to be missed in a case of incipient phthisis confined mostly to the bronchi. Nor should one trial of this measure be regarded as sufficient in a doubtful case, but repeated similar tests should be made.

The diagnostic value of extreme expiration is not confined to the production of râles by the undisturbed flow of air through the narrowed air-channels. Sometimes, if the patient will voluntarily cough at the end of such an expiration, râles will most unexpectedly be brought out that could not occur without it. This test should always be attempted in a doubtful case. The explosive blast of air may, under forced expiration, easily move some phlegm, creating a sound audible to the auscultator, when no amount of deep breathing could produce it.

The limit of possible expiration should be secured, with open-mouth breathing, in making the test (with the fingers or a soft hammer) for cracked-pot percussion sound. This will often produce it to a slight degree when it could not otherwise be developed. I do not undertake to say, amidst the doubt on this point, just what a slight cracked-pot sound always means in disease of the lung, but when it can be produced on one side only, and especially in conjunction with slight râles, even if both are made possible by the manœuvre referred to, it certainly denotes some disease of the part, and that, in beginning cases, is important.

The average patient does not know how to make profound expiration. Tell one to do this, and he will at first as likely take a deep *inspiration*. The human mind, save in the susceptible and very teachable and adaptive years, cannot execute a new sort of muscular evolution off-hand on simply being bid to do it. One must be taught. Profound expiration is such an act; open-mouth normal breathing is another; and in our efforts at teaching them, people are as amusing as they are in that other experience of doctors with them, when bed-patients are asked to turn over on their backs. Fully 99 per cent. of them will turn themselves prone, with their backs uppermost, or start to do it, before they discover their mistake.

In a lung with beginning tubercular deposit in the upper part near the larger bronchi, the vesicular murmur is sometimes lessened over almost the whole lung except the part that lies directly above the deposit, and there is very little expiratory sound, with little of the tubular quality, and few or no râles, while the vocal fremitus is still

moderate in degree, and the percussion resonance is nearly normal, but there is reduced transmission of voice-sounds. There seems no way of explaining such a state of things but by assuming a complete closure of some of the bronchi, by pressure from without or by thickening of their walls or by thick phlegm within them; for the lungs are full of air, as shown by resonance on percussion; there can be no great consolidation, and if tubes are only partially closed there are sure to be râles of some sort, and usually many of them.

Early in most cases of unilateral, localized tuberculosis, some aid to diagnosis may be found in the symptom (usually neglected) of greater cough during recumbency on the affected side. If there is much phlegm, having a fair degree of fluidity, and the local seat of its formation does not reach to the lateral periphery of the lung—and usually in the beginning it does not—it is sure, when the patient lies on the bad side, to run down into the smaller bronchi by gravity, and provoke cough. If he lies on the opposite side gravity carries the product into progressively larger tubes, where it can spread out, its bulk lessened by drying, and adhere to the tube-walls without causing much cough, often for many hours, even to the limit of a night. In the morning the activity of the patient, and perhaps the taking of food and drink, induce a paroxysm or two of cough, and the mucoid accumulations of the night are expelled.

Of course, as soon as the lesion extends to the lateral periphery of the lung, or if it should happen to begin there, so that its tubes and perhaps its air-vesicles are full of fluid, this test will fail. But it must be rare that for this reason it would fail in an incipient case; it more often fails from the paucity of the secretion. It is not at all unusual for this symptom to be pronounced early in the case, and exactly the reverse symptoms be present later, when the air-channels of the periphery of the effected lung become full of muco-pus; and on rational grounds this is what we should expect. The cough, then, is least when lying on the diseased side.

A striking tendency to error in considering chest signs is shown in cases of fluid in the pleural cavity in little children. In a considerable majority of instances this condition is at first overlooked, as it is often missed throughout the whole sickness. This error is not confined to young doctors, but comes often enough to veterans. It comes probably of the double mistake of supposing that the physical signs in

children and adults are the same with given pathological conditions, and in taking too literally in diagnosis certain rules which have grown into the literature and seem altogether rational, but which are unreliable and lead to many pitiable blunders.

Dulness on percussion is a sign in pleural effusion; but in small children there is little or no dulness over the lower part of the chest, especially on the left side; the gas in the stomach and bowels almost completely masks this sign. If the pleural cavity is full to the very apex there is dulness, even flatness, at the top, which, by absence of dulness low down, often leads to the erroneous theory of apical consolidation of the lung.

The books say, and it is a fatally false guide, that the intercostal spaces bulge. They do when the pleura is tense nearly to bursting, once in a hundred cases, not more. Why should such a misleading statement be perpetuated through generations of writings? Why not have said that the intercostal spaces are less depressible and more firm, and been correct and consistent!

It is well understood that lung sounds are not much transmitted through fluid; but over a child's pleural cavity full of fluid faint bronchial breathing is heard. This fact, with the absence of bulging spaces, leads many doctors to dismiss the theory of fluid in the cavity, although vocal fremitus is absent or greatly reduced, and the heart is beating far to the right or left of its normal position. The change in the fremitus (if the bronchi are patulous) must mean fluid or air in the pleural sac, and the heart does not move without assistance; yet we ignore these facts because we hear bronchial sounds or distant murmur, fail to find dulness in the lower chest zone, and the intercostal spaces do not bulge.

THE MICROCOCCUS SUBNORMALIS.

By SAMUEL A. HOPKINS, M.D.

(*From the Bacteriological Laboratory of the Harvard Medical School.*)

PRESENTED BY HAROLD C. ERNST, M.D.,
PROFESSOR OF BACTERIOLOGY, HARVARD UNIVERSITY.

THE mouth-form which is shown in the accompanying photographs is of interest from two points of view: first, from its variable morphology, which I shall refer to later; secondly, from the fact that while it is undoubtedly a mouth-form, though possibly a rare one, it does not grow at the temperature of the body, or, to qualify the statement, it does not grow on artificial media at the body-temperature. Curiously enough, it has happened in my studies of mouth bacteria that I have found several forms that grow more readily at the room- than at the blood-temperature, and in more than one instance have met with micro-organisms in the mouth that would not grow at all in the thermostat.

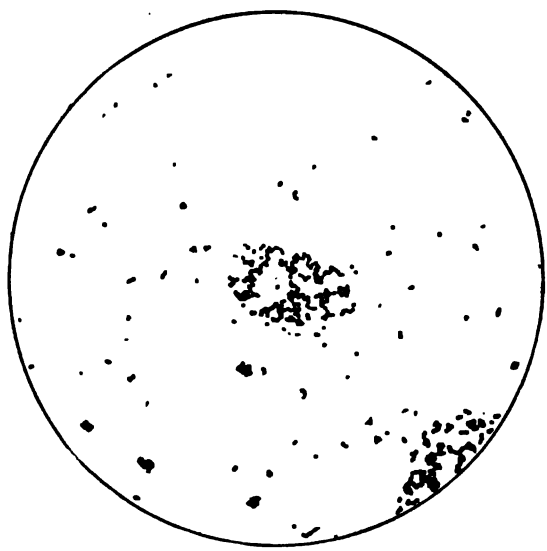
I have no satisfactory explanation of this peculiarity to offer. It suggests the prevalence of the mouth-breathing habit, and points to a possible danger from that source.

When this form was first obtained I was inclined to believe, from the fact that it did not grow at the body-temperature, that it was a transient guest in the mouth of my patient; but when I was able to obtain it from the same mouth after a period of three months, I was forced to believe that it was a more or less constant inhabitant of this particular mouth.

As I have stated, no growth can be obtained at the body-temperature on any of the usual media, but the maximum temperature is only a few degrees below 37° C. It grows best at the room-temperature, but flourishes luxuriantly in the ice-chest at a temperature between 8° and 10° C. Having ascertained this fact, I made cultures on gela-

tin, blood-serum, and potato, and put them in the freezing-room, where the temperature was 28° F., removing them once for examination and putting them back immediately. At the end of three weeks a growth was apparent on the blood-serum and gelatin tubes, not very active, to be sure, but plainly discernible, and cover-glass preparations showed the presence of bacteria in large numbers. All the tubes were then allowed to remain at the room-temperature, and at the end of thirty-six hours a strong growth had appeared on each, and continued to develop as if the cultures had been surrounded by the most favorable conditions. The bouillon tube, which was solid ice at the end of the first week, was found liquid at the end of the third, with a crystalline deposit at the bottom.

FIG. 1.

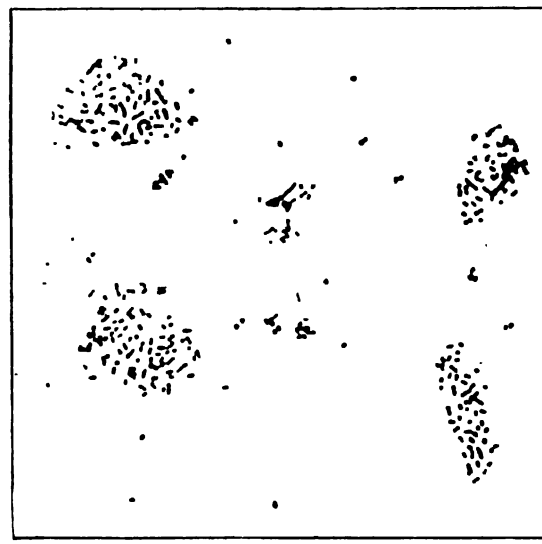


Micrococcus subnormalis, agar.

While the development of this form at such unusual temperatures is of interest, its variable morphology is quite as remarkable. Morphological changes are frequently noticed in micro-organisms from the human mouth. The changes which occur in this one are exceedingly well shown in the accompanying photographs by Mr. John Hubbard.

In studying this organism I was at first exceedingly annoyed by apparent contaminations that kept creeping in to spoil my work, and it was only after several series of plates and many tube cultures had been destroyed that I awoke to the fact that what I had mistaken for contaminations were morphological changes in the organism itself.

FIG. 2.



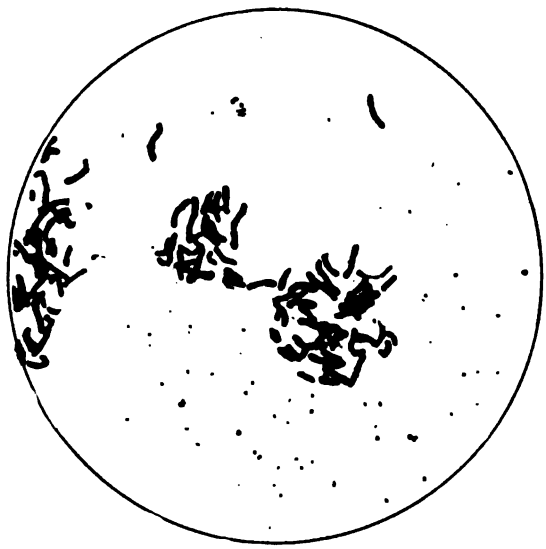
Micrococcus subnormalis. Fresh Löffler blood-serum. Shows lengthening of coccus form and beginning of rod.

To confirm my work, I have had the assistance of Dr. Denny and Dr. Coolidge, of the Bacteriological Laboratory of the Harvard Medical School, for I was still unwilling to rely on my own observations. To Dr. Coolidge I am also indebted for the work on its pathogenic properties, which, I may state, gave negative results. This was presupposed, from the fact that it did not grow at blood-temperature.

Passing over, then, a great deal of preliminary work, we find this round form so difficult to distinguish from a coccus, produced by cultures on agar (Fig. 1) and on Löffler's blood serum, the hard, white, dry blood serum (Fig. 2) being especially adapted to the production of the round form. From this, if we transfer to potato (Fig. 3), we obtain this long, irregular rod form. We also get the rod form on gelatin (Fig. 4), plain blood-serum, and in bouillon. The older

and harder the culture medium is, the greater the tendency toward the coccus form. It would seem as if unfavorable conditions tended to produce a coccus, while favorable conditions, such as fresh, moist culture media and frequent transfers, resulted in a lengthening out into the rod form.

FIG. 3.



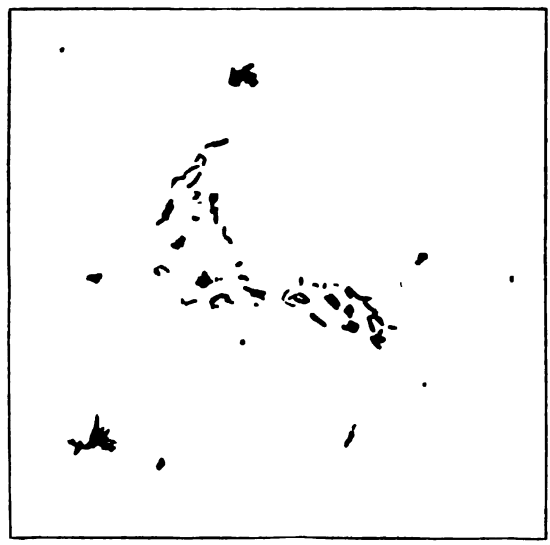
Micrococcus subnormalis, potato.

Authorities agree in drawing a pretty sharp line of demarcation between coccus and rod forms, and Abbott voices the general opinion when he says, "One can never produce bacilli from micrococci, or *vice versa*, and any evidence that may be produced to the contrary is based upon untrustworthy methods of observation." In view of the kaleidoscopic changes that are going on in every branch of science, I think this a bold statement to make. If bacteria, though almost submicroscopic, are still subject to the laws which control the origin and development of the higher vegetable orders, then we have only to bear in mind the differences which mark the growth of these higher orders to appreciate that remarkable changes are possible in these microscopic plants. It is not positively asserted that a rod can be produced from a coccus or a coccus from a rod. Careful examination will show in the coccus form a slight lengthening of one diameter,

while the rod is not perfect in outline, and sometimes has the appearance of being made up of several cocci jammed together.

It is asserted, however, that many forms described as cocci are less spherical than the one I have described, while our present knowledge would certainly classify this longer form as a rod.

FIG. 4.



Micrococcus subnormalis, gelatin.

In other respects this bacterium does not differ from others well-known. Its color, which can best be seen by daylight, is a deep lemon-yellow, varying somewhat on different media, and reaching its highest intensity on blood-serum and potato. The color is developed by exposure to light, cultures placed in a dark place having a dirty gray appearance. It may be said in passing that chromogenic bacteria are extremely common in the human mouth. In my work I have isolated no less than eight different varieties of mouth-forms giving a yellow color, and there are several more which I have not yet had time to study. This one is easily cultivated; it stains readily with nearly all the usual stains, appears to be non-motile, and does not produce spores. In conclusion I will say that I have not established a definite law governing the growth of this bac-

terium. There are certain indications that point to the possibility of the rod being made up by the union of several of the round forms, but further study will be necessary to establish this as a fact. The chemical differences which exist in culture media may be responsible for some of its peculiarities, but these differences are too subtle to be readily understood. The tentative name of micrococcus subnormalis has been given to this organism.

ON THE SIGNIFICANCE OF JAUNDICE IN TYPHOID FEVER, AND ON THE HEPATIC COMPLICATIONS WITHOUT JAUNDICE.

By J. M. Da COSTA, M.D., LL.D. (Harv.),
of Philadelphia.

During the past winter there were in the wards at the Pennsylvania Hospital a number of cases of typhoid fever that presented the peculiar and rare symptom, jaundice. It is the object of this paper to analyze these cases and to inquire into the significance of jaundice when occurring in typhoid fever, at the same time that the hepatic complications in which jaundice does not generally happen will be passed in review.

Case I.—A colored woman, aged eighteen years, was in the ward for a long time, extremely ill with typhoid fever. The course of the fever was marked by only moderate diarrhœa, but it was attended with very high temperature, the record showing temperatures of 105° and upward, and by nervous manifestations, especially delirium; the Widal reaction was decided. In this case of long-continued typhoid fever there appeared two striking symptoms: one was jaundice, the second was inflammation of the right parotid gland.

The jaundice appeared on the eleventh day of the disease, and though by the thirtieth it had greatly diminished, yellowness was still perceived in the conjunctivæ. The jaundice was not associated with any marked change in the size of the liver; if there were any, it was slightly increased, for the percussion dulness was distinctly to be detected below the margin of the ribs; the organ was painful to the touch when pressure was made over its free border, and there was general sensitiveness of the abdomen.

Subsequent to this state of things the right parotid gland gave evidence of inflammation, and became tumid and tender. The swelling at the angle of the jaw subsided without suppuration under local treatment with ice and applications of tincture of iodine, and by the thirtieth day of the disease there was very little to be felt of the parotid swelling, which at one time threatened to form an abscess. As further symptoms in the case may be noted nausea and vomiting, hebetude, and albuminous urine showing blood-cells and granular and hyaline casts, as well as pus casts and bile-stained

epithelial cells. The urine was freely passed, forty-six ounces in twenty-four hours, and contained one-half gramme of albumin to the litre; it responded readily to the tests both for biliverdin and bilirubin. On several occasions chills occurred, but they were not severe; the blood was examined for malarial organisms, with negative results.

Jaundice persisted, though slight, for a few days more; the tenderness over the lower part of the liver disappeared; the bowels were constipated; the tongue was somewhat coated; the temperature was 99°. The urine, tested repeatedly when the jaundice was at its height, gave evidence of the presence of bile-pigment. The stools were never clay-colored; indeed, they were usually the ordinary stools of typhoid fever; sometimes they were noted as brown, sometimes as yellow or greenish. No bile-pigment was detected in the urine on March 7th, the thirty-second day of the disease. The patient made a good, though slow, convalescence.

It is worthy of note that the jaundice was associated with parotid swelling, which I think more than a coincidence, as it has happened in other instances, as we shall further on see.

Let me now give the particulars of a case of jaundice in typhoid fever which came on very late in the disease, only three or four days before death, and grew in intensity to the fatal ending.

CASE II.—Sarah K. B., aged thirty years, white, was admitted February 18, 1898, with the statement that thirteen days previously she had been taken ill with anorexia, diarrhœa, vomiting, and epistaxis. She had not had a chill, headache, or cough. Upon admission her temperature was 104°, the pulse 120, the respirations were 40 to the minute. Her cheeks were flushed, the pupils were large, the sclera clear, the conjunctivæ of a good color. Sordes existed upon the teeth and lips. The tongue was dry, red at the tips and edges, with a brown streak in the centre. Her breath was fetid. The lungs were clear on percussion; there were no râles. At the apex of the heart was heard a blowing systolic murmur, not transmitted; at the base, too, was a soft, blowing systolic murmur, which was transmitted into the carotids; there was no venous hum. The heart's action was regular but rapid. The pulse was small in volume and dicrotic. The liver-dulness began at the sixth rib and extended to the costal margin; the border was not palpable. The spleen extended from the eighth rib in the mid-axillary line to the last rib; it was not palpable, and not tender upon percussion. The abdomen was tympanitic, and, upon pressure, pain and gurgling were elicited in the right iliac fossa. Characteristic rose-spots were found on the abdominal surface. There were pre-tibial œdema and some pain upon pressure in the legs.

On the following day it was noted that hebetude was marked, the facial expression was dull, the temperature was 102° to 103°, the pulse very weak, dicrotic, and compressible. The urine was straw-colored, with an abundant sediment; it was acid, of specific gravity 1030, and contained a trace of albumin, with abundant urates and granular and hyaline casts.

The treatment was beta-naphtol, three grains every third hour; whiskey, a half-ounce every second hour; strychnine sulphate, one-thirtieth of a grain every fourth hour, and a milk diet. The surface of the body was sponged with cold water every third hour, when the temperature was 103° or over.

During the next few days the bowel movements continued loose and frequent, from four to seven daily. The eruption became more profuse. The temperature was only kept down by systematic sponging. The splenic area of dulness became much increased, and some local tenderness developed; the tongue became dry, brown, and fissured. The Widal test of the blood yielded a positive reaction. The stimulant was increased to five drachms every two hours on the 21st, on account of the very dicrotic character of the pulse; but as this was better the next day the whiskey was decreased to four drachms every two hours. The hebetude continued; there was epistaxis on the 23d. On the 24th the pulse was noted as stronger and more regular, though still rapid. A systolic murmur, looked upon as hæmic, persisted. There was marked throbbing of the carotids; the second cardiac sound was distinct. She was weak and exhausted, at times delirious, though the mind was mostly clear. On the 25th some yellowness of the conjunctivæ was observed, and the urine contained bile-pigment. On the 26th it was noted that the skin and conjunctivæ were markedly jaundiced. The pulse was feeble and compressible. The bowels were very loose, eight movements within the last twenty-four hours, notwithstanding the use of opium suppositories; the discharges were thin and yellow. Dilute nitro-muriatic acid, fifteen minims, was given every four hours in place of the beta-naphtol, which had been discontinued. Oxygen inhalations were also employed, and she took strychnine.

On the 28th the records state that the delirium was deepening. She was intensely jaundiced all over the body. The eruption was still profuse; the liver was not enlarged or palpable; there was no pain or soreness over it. The pulse was very weak; sordes were present on the teeth and tongue; the bowel movements were green and yellow, and still loose. In spite of very free stimulation, the patient died of exhaustion during the evening. An autopsy was not obtained.

In the cases that have been detailed the jaundice occurred as a late symptom. Jaundice may be, however, an early symptom, and even show itself in advance of the fever, appearing as the result of an early infective process in the bile-ducts.

In a remarkable case which, so far as I know, is unique, the jaundice distinctly preceded the development of the typhoid fever, and occurred during the latter part of the period of incubation.

CASE III.—A Danish weaver was admitted into my ward at the hospital on January 7, 1884. He had been jaundiced for a few days without obvious cause. He complained of weakness and loss of appetite. His temperature was 99.5°, the pulse 118. The next day the yellowness of the conjunctivæ

and the skin was more marked; the tongue had a heavy yellow coat; the liver was observed to be somewhat enlarged, as was the spleen. The case was looked upon as one of catarrhal jaundice, and he was treated with phosphate of sodium and Rochelle salts, and placed on a restricted diet. The jaundice slowly improved and almost passed away, but the man did not get well, for, after the 19th, he was noticed to be decidedly feverish, and on the 24th the morning temperature was 104°, and he was very weak; his face was flushed; diarrhœa set in. A note made at this time states that he had all the appearances of beginning typhoid fever. On the 27th there was no doubt of the correctness of this view. The tongue was coated, with red edges and tips. The abdomen was tympanitic, the movements from the bowels loose and of typhoid character. Rose-colored spots were found on the abdomen. He had repeated epistaxis.

He was treated with eight grains of quinine daily, with stimulus, with dilute muriatic acid, and, later, with turpentine. In the course of the case great restlessness, delirium, and subsultus tendinum were noted, followed by marked hebetude, increasing prostration, and frequent involuntary movements from the bowels. He died February 4th, from exhaustion.

At the autopsy the liver was found to weigh four pounds, eight ounces. The gall-bladder contained thin, pale-colored bile; there was no evidence of inflammation or ulceration of its mucous membrane, or of disease of the bile-ducts. The hepatic cells showed a cloudy swelling; the same condition was noticed in the epithelium of the kidneys, which were otherwise healthy. The spleen weighed twenty ounces, was highly congested, and its tissues soft. The posterior portions of the lungs were much congested. A number of infiltrated and ulcerated Peyer's patches were found in the lowest part of the ileum. There was also ulceration of many of the glands of the large intestine, and considerable swelling of the glands of the mesentery.

It is difficult in this case to state exactly when the typhoid fever began, but, counting from the appearance of the eruption, which we know to be between the seventh and ninth days, the fever probably started on the 18th or 19th of January, and thus about two weeks after the onset of the jaundice. This, therefore, would be strictly within the period of incubation, and it seems reasonable to suppose that the typhoid infection had lighted up a catarrhal process in the gall-bladder and bile-ducts which antedated the intestinal affection and disappeared in the course of the febrile malady. The alternative suggestion is coincidence, which seems very unlikely.

The case of jaundice in typhoid fever that I shall now describe was admitted into the Pennsylvania Hospital on January 31, 1898, the day on which I gave up the men's medical ward to my colleague, Dr. Arthur V. Meigs, who kindly permits me to give the details of the case as it developed under his observation.

CASE IV.—J. S, a waiter, aged twenty-six years, was admitted into the hospital with the distinct statement that he had never had pneumonia, an affection of the liver, rheumatism, or typhoid fever. He had been ill for ten days previous to admission, and a week before his admission he was seized with a severe chill, followed by fever, sweats, and epigastric pains. From this time on he had a number of chills, with severe abdominal pains, most acute over the region of the gall-bladder, accompanied by obstinate constipation and vomiting. When examined on admission his temperature was 102.2°, the pulse 88; the skin and conjunctivæ were decidedly jaundiced; the tongue was heavily coated; the abdomen rigid, not distended, but generally painful on percussion. There was no particular tenderness in the right iliac fossa; the greatest tenderness was over the region of the gall-bladder, and pressure there caused nausea. The liver was distinctly enlarged and palpable. A considerable amount of urine was drawn by catheter. The man lay in bed with his legs flexed and with all the appearances of a local peritonitis. Poultices were applied to the abdomen without material modification of the symptoms. On the evening of the first day the temperature attained to 104.4°. It declined to 98.6° the next morning, and then passed by evening to 103°. On the second day after admission it had fallen early in the morning to 99°. The patient was extremely restless, with clammy perspirations, the pulse was imperceptible, and he soon died.

His case suggested an inflammatory disease within the abdomen rather than typhoid fever, and the symptoms were such as might have been due to an appendicitis at the upper part of the appendix.

At the autopsy typical typhoid ulcers were found in the ileum and cæcum, the mesenteric glands were swollen, the spleen was large and friable; there was no peritonitis. The liver was considerably enlarged; its left lobe had a blunt edge. There was no abscess or gross lesion in the liver. The gall-bladder was distended with an unhealthy-looking bile; it contained no concretions; its coats were not altered; it had no adhesions. There was no swelling or sign of inflammation in the biliary ducts. The base of the right lung was congested.

It appeared at first from the symptoms that the case was one of cholecystitis; the nausea and vomiting, and especially the seat of pain, pointed to it. But the autopsy did not bear out this view, since no signs of inflammation of the gall-bladder were found. The distention of the viscus was the only thing to account for the pain; and the jaundice must, after all, have been the result of the blood alteration and the morbid condition of the liver structure. It is to be regretted that there are no microscopical or bacteriological examinations to record.

In the case we have just examined the jaundice was associated with the occurrence of chills; indeed these formed a prominent feature of the morbid manifestations. They were yet more so in the following case, though the lesion was, I believe, a different one. The man was

shown at a clinic with great enlargement of the spleen in the course of typhoid fever, and the jaundice subsequently developed in the midst of very grave symptoms.

CASE V.—A Swedish sailor, aged twenty-three years, was admitted on December 6, 1897, with severe abdominal pain, that was at first over the whole upper part of the abdomen, but had localized itself in the left hypochondrium, extending almost to the crest of the ileum. The temperature was 99.6°. The bowels were moved two or three times daily; the discharges were not loose. The pulse was 120, weak, and irregular; the tongue markedly coated and tremulous. The history obtained was that he had been an unusually healthy man who did not remember any illness except an attack of malaria some years ago. Eight weeks since, while at sea, he began to suffer with headache and weakness; subsequently was seized with fever; was delirious part of the time, and altogether decidedly ill for weeks on board ship. He was very weak when he left the ship, but after reaching land he began to improve until the last few days, when he had night-sweats, abdominal cramps, and felt himself very ill. The day of admission the temperature rose in the evening to 104.2°; no rose-spots were found. The most marked feature of the case was the extent of the splenic dulness, which was 18 cm. in length from the sixth rib laterally, and passed fully two fingers'-breadth below the costal margin. The enlarged organ could be distinctly felt, and was very tender on pressure; indeed, the whole splenic region was tender to the touch, extremely so on percussion. Bulging was visible to the eye, and the line of dulness was influenced by inspiration and expiration. The heart's action was rapid, the second sound accentuated; there was no murmur; marked pulsation existed at the supra-clavicular notch.

He was looked upon as having typhoid fever with splenitis, and the question of abscess of the spleen was considered. There was some doubt whether we were dealing with the primary attack of the fever, prolonged by the condition of the spleen, or with a relapse; the former view was adopted. The patient was placed on dilute muriatic acid, twenty minims every fourth hour, on milk-diet, and the ointment of iodide of mercury and lanolin, equal parts, with four grains of extract of belladonna, was rubbed in over the spleen. The blood examined microscopically showed 4,500,000 red to 6000 white corpuscles. Widal's reaction was positive. The urine was acid, of specific gravity 1029, and contained neither sugar, nor albumin, nor casts.

On December 9th, three days after admission, a crop of rose-spots was found on the abdomen. These disappeared by the 13th; his whole condition was steadily improving and the temperature had become normal A note on the 16th speaks of the large size of the spleen persisting, but of the tenderness having gone; of the absence of tympany, of tension of the abdomen, and of any signs of cardiac disease. On the 17th the temperature began to rise, and by the evening of the 18th it had attained to 105°; the pulse was 148, and weak; the respirations were 40. There was a slight return of the splenic tenderness, but nothing marked. The blood was examined for plas-

modium; none was found. Dark days followed, with recurring severe chills and temperature of 106°, with a pulse weak and 156; with hurried, shallow breathing and congested lungs, but with the murmur remaining vesicular. The first sound of the heart was indistinct, the second clearer and well defined. In the blood, repeatedly examined, no plasmodium was detected; a repetition of Widal's test gave again the same positive result. Quinine in large doses produced no effect on the chills, and but little on the temperature. A cold bath reduced it to 95°, but he did not bear the bath well. The temperature rose again by the next day to 105.3°, and two chills happened on that day. After the chills and the fever rises the patient did not sweat, but the skin was moist. A note of the 21st mentions yellowness of the skin and the conjunctivæ, and bile in a urine free from sugar, but slightly albuminous and containing hyaline and granular casts. There was no distention of the gall-bladder; the lower border of the liver could be felt, and was slightly tender; the organ extended just below the margin of the ribs. General abdominal pain existed at the upper part of the abdomen; the stools were not clay-colored.

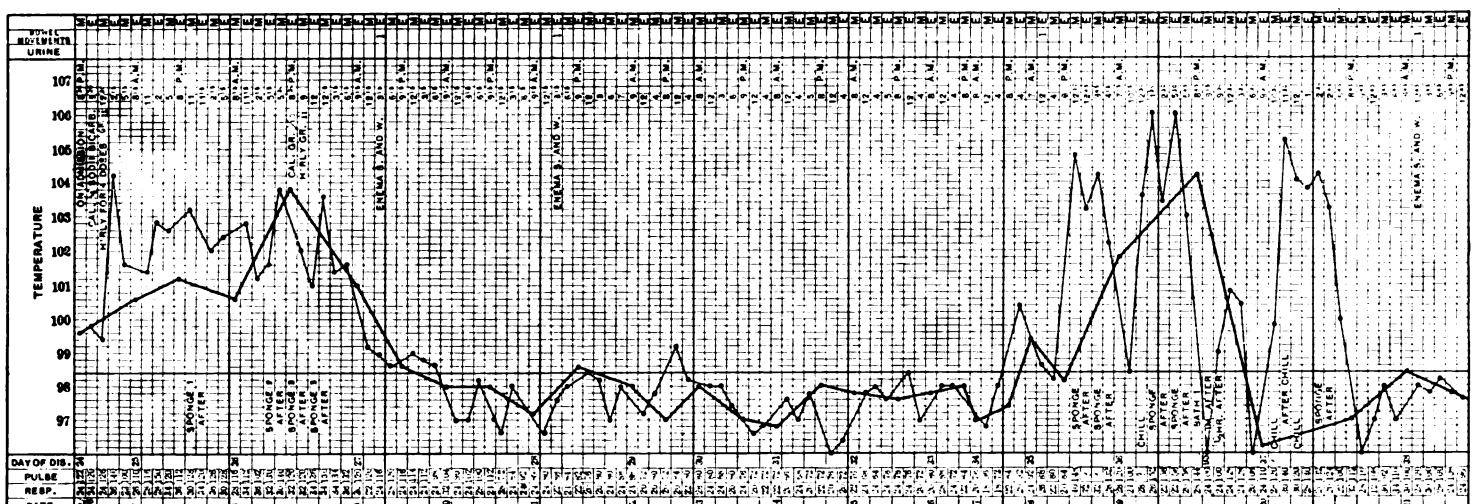
During the time of the chills and fever and at the height of the jaundice the treatment consisted chiefly of sixteen grains of quinine daily, and of borate of sodium, ten grains every third hour, given for a time in place of the dilute muriatic acid, which, however, was afterward resumed; and, while the temperature was so high, three grains of phenacetin, with two of salol, were also administered with some apparent effect. For a time, too, the weakness of the circulation necessitated the free use of digitalis and of whiskey.

The temperature, by the 21st, became normal and remained so with occasional exacerbations during convalescence. There was, however, from January 2d to the 10th, a post-typhoid temperature reaching 102°, without return of the eruption. The splenic dulness gradually decreased, and by the 5th extended merely to the margin of the ribs; the jaundice had entirely disappeared by the 5th, even to the urinary tests. The man left the hospital well on January 26th.

It is very difficult to explain this case. As regards the spleen, there was no doubt of its great enlargement and tenderness, more marked than I have ever seen in typhoid fever, and I looked throughout the case for an abscess. But no positive evidence of this was ever obtained, and if it happened, or a purulent infarction occurred—which, as Murchison noticed in two cases, softened—the purulent fluid was absorbed or encapsulated, and no rupture took place.

Regarding the spleen as the source of the grave symptoms, two views suggest themselves to account for the chills and the jaundice. One is that they were both pyæmic from the morbid process in the spleen, the jaundice being of blood origin, as it is in pyæmia. The second is that, considering the splenic vein as a main branch that goes to form the

Temperature Chart of Case V.



The lighter lines represent the intermediate temperatures.

portal vein, infected thrombi produced a pylephlebitis, and that chills and jaundice, the latter certainly, resulted from the superinduced condition of the portal vein. The difficulty of adopting this view is the recovery. Still, we know that pylephlebitis may end in recovery. Frerichs tells us that this may happen when the pylephlebitis is not too extensive. In a recent operation for typhlitis Treves[1] actually saw the morbid lesions. The liver surface was dotted over with the innumerable yellow specks regarded as characteristic of the disease, and the patient's condition appeared hopeless, but she recovered. On the whole, I believe that the view of the patient whose case I have been describing having had pylephlebitis is the correct one.

Jaundice is of very rare occurrence in typhoid fever. Sir William Jenner[2] states that he has never observed a case. Murchison[3] has met with it in but four instances, and had a fifth case communicated to him. My friend and late colleague at the Pennsylvania Hospital, James H. Hutchinson, reviewing his experience in typhoid fever in an excellent article,[4] mentions that he had not seen this complication. Petrina,[5] during the years 1875 to 1880, met with but one case in 194 deaths from typhoid fever. Griesinger is quoted by Liebermeister[6] as having noted it ten times in 600 cases, and Liebermeister mentions that in the hospital at Basle it was observed twenty-six times in 1420 cases, or one in about fifty-five. These figures indicate higher proportions than jaundice is generally regarded as occurring in, except in hot climates. Jamieson[7] states that in China it is generally, perhaps always, present to a greater or less extent in prolonged cases, and cites nine cases in which it was deep. But Sorel,[8] in Algeria, observed only six cases in 871 of typhoid fever. In cold climates jaundice in typhoid fever must be very rare. Huss,[9] in analyzing 2294 cases of typhus abdominalis—typhoid fever—in Stockholm, does not mention an instance. Yet Werner,[10] in St. Petersburg, speaks of having observed ten cases in one outbreak of typhoid fever.

Prior to this winter I had met with but a solitary instance that I can recall, and it is remarkable that this paper, which contributes five to the scanty general number, should record four observed in the last

[1] British Medical Journal, February, 1894.
[2] On Fevers and Diphtheria.
[3] Diseases of the Liver, 2d ed., 1877, p. 401.
[4] System of Practical Medicine by American Authors, vol. i. p. 295.
[5] Prag. med. Wochenschrift, 1881, No. 41–43.
[6] Ziemssen's Cyclopædia of the Practice of Medicine, vol. i.
[7] Imperial Maritime Customs, China Med. Reports, 1888–95, 37th Issue, pp. 63, 67.
[8] Bull. et Mém. de la Société Méd. des Hôpitaux de Paris, 1889, tome vi. 3d series.
[9] Statistics and Treatment of Typhus and Typhoid Fever, etc., 1855.
[10] St. Petersburger med. Wochenschrift, 1892, p. 32.

few months, during which we have had a widespread epidemic of typhoid fever in Philadelphia. Where there is a complication of malaria, jaundice is not infrequent. Thus, in the report of so-called typho-malarial fever from the Seminary Hospital during the civil war, jaundice occurred in seven out of 64 cases, only one case of which was fatal.

As regards the time of the occurrence of the jaundice, it generally does not come on until the middle of or until late in the disease. In my own cases, omitting Case III., where it antedated the febrile malady, it began in one case (Case I.) on the eleventh day; in Case II., on the twenty-third day; in Case IV. it probably came on in the first week; in Case V., as convalescence seemed to have been reached. In most of the instances on record that I have analyzed, it appeared in the second or third week of the disease. Still the jaundice may happen early, as it did in many of Jamieson's cases.[2] In one of Andral's fatal cases[3] it occurred on the third day; in a fatal case of Frerichs',[4] on the fifth; in one of Murchison's[5] that recovered, it appeared on the sixth day of a relapse; in one of Osler's[6] cases, also ending in recovery, on the fourth day of a relapse; in one of Sorel's[7] cases, not until convalescence; in McPhedran's case,[8] just before convalescence. It may go on, and is apt to go on, gradually deepening until death, and may—though this is very exceptional—become dark and intense. In cases that recover the jaundice gradually disappears with the fever; yet it may persist into convalescence, as in Case I. of this paper, and even remain after the patient is able to be about.[9]

With reference to the symptoms that attend the jaundice, we do not find that they are constant; they are, as a rule, the symptoms of a severe case of typhoid fever with the usual amount of tympany and nervous disturbance. Delirium is apt to be present; yet I cannot say that it has seemed to me much aggravated by the hepatic condition, and there are intervals of clear mind even in the delirious patients, as happened in Case IV. and in Case V., in which questions are answered rationally. The temperatures are, as a rule, high, and, as the cases here presented prove, chills are not uncommon; nor are pulmonary congestions. Vomiting is a frequent but far from invariable symptom.

[1] Medical and Surgical History. Medical History, part iii. p. 305.
[2] Loc. cit.
[3] Clinique Méd., 1834, vol. i.
[4] Diseases of the Liver, 1858.
[5] Diseases of the Liver, Case CXXXVII.
[6] Case I., Transactions of the Association of American Physicians, vol. xii., 1897, p. 380.
[7] Société Méd. des Hôpitaux, tome vi.
[8] Canadian Practitioner, March, 1891.
[9] Case XXXVIII. in Murchison, Treatise on the Diseases of the Liver.

The urine almost always contains bile, and, as in grave cases of typhoid fever, is apt to show some albumin and granular and hyaline casts. Examined by Murchison,[1] in two cases, for leucin and tyrosin, these were not found. The character of the stools is of special interest; they are much like the ordinary typhoid stools, or darker and greenish; they are very rarely clay-colored. In four of the five cases here reported they were not. But in one of Murchison's[2] cases in which jaundice happened during a relapse, the stools were noticed as clay-colored, and the same in Osler's[3] case in which jaundice appeared early in a relapse. There may be, as in one of Andral's[4] cases, marked constipation. Neither the temperature nor the pulse has appeared to me to be influenced by the occurrence of the jaundice; the temperature remains high, the pulse rapid. In some instances profuse sweats occur. The liver is generally somewhat sensitive to the touch, especially at its lower border. In the cases I have noted it was slightly enlarged or of normal size. But it has been observed to be much reduced, as in the case reported by Sabourin;[5] in the case mentioned by Frerichs, the hepatic dulness was almost absent.[6]

Complications attending the cases in which jaundice is met with are not unusual. Marked pulmonary engorgement existed in Cases IV. and V. detailed in this paper. In one of Andral's[7] cases the patient died of left-sided pneumonia on the ninth day of the disease; both lungs were highly congested. In a case described by Louis[8] in which jaundice and bilious vomiting occurred, there was a purulent swelling of the right parotid; abscesses were found in the liver. In the first case of my series there was also parotid swelling, but it did not suppurate. In Sander's[9] case double parotitis followed, and the number of cases of combination of jaundice with parotitis in typhoid fever shows that it is more than coincidence. In one of Frerichs' cases,[10] too, parotitis is mentioned, but it was associated with typhus rather than with typhoid, and, therefore, cannot be, strictly speaking, considered here. In another[11] of his cases of jaundice in undoubted typhoid, profuse epistaxis preceded the jaundice, as it did in Case II. of my series. In Lannois' case[12] the epistaxis was marked and repeated; the jaundice was very intense,

[1] Ibid., p. 420.
[2] Diseases of the Liver, Case CXXXVII.
[3] Loc. cit., p. 380.
[4] Clinique Méd., 1834, vol. i. p. 11.
[5] Revue de Médecine, 1882, p. 600.
[6] Observ. XVIII., Diseases of the Liver, vol. i., Sydenh. Soc. Trans., p. 215.
[7] Clinique Médicale, 1834, tome i. p. 11.
[8] Fièvre Typhoïde, vol. i., Observ. XVII., p. 111.
[9] Deutsche Klinik, 1861, p. 70.
[10] Diseases of the Liver, p. 168.
[11] Ibid., Observ. XVIII., p. 215.
[12] Revue de Méd., 1895, p. 911.

black. Epistaxis, indeed, bears, I think, a distinct relation to the jaundice and its intensity. In one of Murchison's[1] cases thrombosis of the femoral vein happened in a patient who had become jaundiced on the fourteenth day of enteric fever. In Freundlich's case[2] thrombosis of the scrotal veins and gangrene of the left inguinal region coexisted. He had also double croupous pneumonia of the lower lobes. When jaundice is severe and occurs early, Jamieson[3] speaks of its usual association with hæmoglobinuria, intestinal hemorrhage, and hæmatemesis —indications of blood dissolution.

Having examined into the mode of appearance of the jaundice and the symptoms attending it, let us inquire into its origin. Is it a jaundice of obstruction to the flow of bile, such as we know catarrhal jaundice to be, or is it due to the blood condition and the changes in the parenchymatous structure of the liver? In the great majority of instances, most assuredly, I think, not to the former condition. It is usually a blood jaundice, with more or less disorganization of the red corpuscles and often associated with alteration in the liver cells. In favor of this view we have these facts: its occurrence, as a rule, as a late symptom and in grave cases; the character of the stools, which are but little modified, and do not show any hinderance to the flow of bile; the general similarity to the jaundice noticed in other infective diseases and altered blood states, such as in pyæmia. The condition of the liver itself does not give us much information. Yet where the organ has been carefully examined it has been found to show degeneration, granular or fatty, of the hepatic cells, that has even been likened by Frerichs to the state found in acute atrophy. Then in some instances we have abscess, though not in many, for I shall presently show that in the majority of cases abscess of the liver attendant on typhoid fever is not accompanied by jaundice. Further, we may have a pylephlebitis, with secondary changes in the hepatic tissue. However different, these causes may be all grouped together as non-obstructive jaundice—jaundice not from catarrhal obstruction of the bile-ducts. In a few instances this, however, does happen, and the records submitted in this paper prove that it is especially as a precursor to the active development of the enteric fever (as in Case III. of my own cases), or in the early stage of a relapse, that this kind of jaundice occurs.

Broadly speaking, then, the jaundice met with in enteric fever is due to the blood affection and the alterations produced by the toxins of the disease in the secreting cells of the liver, or to gross changes otherwise

[1] Diseases of the Liver, 2d ed., Observ. CXXIX., p. 420.
[2] Deutsche Archiv für klin. Med., Bd. xxxiii., 1883, p. 318.
[3] Loc. cit., p. 63.

there induced, and only in exceptional instances to a catarrhal condition of the bile-ducts. Besides this, jaundice in typhoid fever occurs from inflammation of the gall-bladder and the morbid changes in the bile-ducts that may attend the cholecystitis. But this I only mention here to enumerate all the causes, as we shall presently examine this disease in detail.

It is apparent that jaundice in typhoid fever is not always associated with the same lesion, and that we can no more regard it as significant of any one hepatic disorder than we can jaundice met with in the varied diseases of the liver and bile passages unconnected with typhoid fever. Further on, I shall endeavor to make clear in how far we can, with reasonable certainty, distinguish between the different causes of jaundice in typhoid fever; but for the present I again state that the most frequent cause is from the blood infection, and without gross organic lesion, though in a moderate proportion of cases this exists.

Taking this general view of the subject, let us inquire into the gravity of the symptom. It is, indeed, a grave symptom, as may be judged from the following table, in which I have placed, together with my own cases, those in which there is sufficient detail to make them of any clinical value, and excluding the cases associated with perforation of the gall-bladder and other very marked gall-bladder lesions, which I shall speak of separately.

We have thus, in 52 cases, 33 deaths and 19 recoveries. Analyzing further these cases, according to their probable cause, we find them thus grouped: 4 catarrhal; 3 pylephlebitis, of which in one (the case of McPhedran) there were also marked changes in the liver; 5 of cholecystitis, in 2 of which (the cases of Sander and of Griesinger) there was most probably, too, cholangitis; 6 cases of abscess of the liver; 5 of acute yellow atrophy or a state closely akin to it (2 of Frerichs, 2 of Murchison, and 1 of Sabourin), and 29 cases in which blood infection and more or less of a fine parenchymatous change in the liver existed; of these, 5 (Sorel's) are not fully enough reported for us to be certain as to the cause of the jaundice, and, for the sake of accuracy, cannot be counted, leaving 24 in which the condition just mentioned was either proved or may be with reasonable certainty assumed to have existed. It would be very desirable to separate those in which there is a mere blood infection, induced by the presence of the typhoid bacilli or their toxins in the blood, or the absorption of septic matter with or without infected thrombi, and leading to alterations in the blood-corpuscles, from those in which decided, though not gross, parenchymatous changes happen. But it is impossible to do so with any certainty. Moreover, there is no fixed line; changes in the liver texture are soon secondarily induced.

Looking at the results, according to the best-ascertained cause of the jaundice, we note in the four catarrhal cases three recoveries and one death, this being the catarrhal case of my series, which, however, died a considerable time after the disappearance of the jaundice. In the three cases of pylephlebitis we find one recovery and two deaths; in the five cases of cholecystitis with jaundice there were two recoveries and three deaths; in six cases of abscess of the liver, one recovery and five deaths; of the five cases of yellow atrophy all died.

The most common of the ordinary and lighter changes in the liver structure consists in a cloudy swelling, with granular degeneration in the hepatic cells. But Handford,[1] while mentioning that both parenchymatous and interstitial changes are frequently found, regards as the most constant and, perhaps, the most important of these, interstitial hepatitis. This may, as a sequence, lead to atrophic cirrhosis, as in a case reported by Bourdillon.[2] The little opaque areas of destroyed liver-cells, that were formerly described as lymphoid nodules, and are not uncommon, do not, so far as is known, give rise to any symptoms pointing to the necrotic change.

The question may arise whether the jaundice may not be due to some agent employed in the treatment. But it has been observed under the most diversified, including the cold bath, treatment.[3] Werner,[4] who is an advocate of the use of chloroform in typhoid fever, states that he observed jaundice in four cases, very light in three, without swelling or tenderness of the liver, and stopped the remedy. But in six other cases treated with chloroform later, also in boys under fifteen years of age, notwithstanding the longer use of the remedy, jaundice did not occur.

Jaundice in typhoid fever happens most often at the *age* at which typhoid fever usually happens. But Petrina[5] reports a case in a woman aged fifty-six years; Burder,[6] one in a boy aged nine years. I do not know of a single instance in early childhood. As regards *sex*, many more cases have been met with in men than in women.

The main object of this paper is the consideration of the clinical significance of jaundice in typhoid fever, and this has now been done. But it would be incomplete without inquiring into the frequency with which jaundice is absent, though hepatic complications exist, and with-

[1] Hepatitis in Enteric Fever. Trans. Path. Soc. London, 1889.
[2] La Semaine Médicale, September 30, 1891.
[3] Goltdammer mentions two such cases. Deutsch. Arch. f. k. Med., 1877, Bd. xx. p. 68.
[4] St. Petersburger med. Wochenschrift, 1892, p. 32.
[5] Prager med. Wochenschrift, 1881, Nos. 41 and 43.
[6] Lancet, October 17, 1874, p. 552.

TABLE OF FIFTY-TWO CASES OF JAUNDICE OBSERVED IN TYPHOID FEVER, WITH RESULTS.

No.	Author.	Reference.	No of cases.	Probable cause of jaundice.	Marked associate symptoms.	Result.	Post-mortem appearances.	Remarks.
1	Andral	Clinique Médicale, 1834, vol. i. pp. 10, 616.	2	Blood infection	In the first case pneumonia of left lung; heavy congestion of both lungs. In the second case jaundice very marked.	Died.	In both cases lesions of typhoid fever; condition of liver not stated in first case. In second nothing abnormal was seen in liver and biliary passages.	
2	Louis	Fièvre Typhoïde, 1841, vol. i. obs. xvii. p. 118, and obs. xxvi. p. 369.	2	Blood infection and liver abscess in first case; blood infection in second case.	In the first case suppurating parotid gland; pain in the sides and in epigastrium; bilious vomiting; marked delirium. In the second case jaundice on the twenty-fifth day of the disease, preceded by erysipelas of leg.	Died.	Typhoid fever lesions in intestines; enlarged mesenteric glands; an abscess near the free border of the liver; six smaller masses (metastatic abscesses?) in the small and middle lobes; bile passages healthy. In second case many typhoid fever ulcers; softened mesenteric glands; healthy liver and biliary ducts; distended gall-bladder.	
3	Frerichs	Diseases of the Liver, obs. xiii., 1858, obs. xviii.	2	Blood infection and parenchymatous change in liver (like acute yellow atrophy).	Great tenderness in region of liver, and afterward of entire abdomen; thin greenish stools; bilious vomiting; chill, dyspnœa. In the second case chill; thin, pale stools; violent epistaxis; tremor; dyspnœa; diminution of hepatic dulness.	Died.	Typhoid ulcers in ileum; débris of disintegrated cells, oil globules in the portions of softened liver; liver yielded leucin and tyrosin abundantly; gall-bladder not affected. In the second case liver shrivelled; disintegrat'n of hepatic cells, some filled with fat; mucous membrane of gall-bladder not affected; small quantities of whitish fluid in gall-bladder.	
4	Sander	Deutsch. Klin., 1861, p. 70.	1	Cholecystitis and probably cholangitis.	Jaundice appeared at end of second week; became very marked; vomiting; grayish stools; severe pain like bilious colic; tenderness in hepatic region and enlargement of liver; after five or six days gradual disappearance of the jaundice.	Died.	Biliary ducts were found to be dilated, and a large number of stones were in the gall-bladder.	After having entered on convalescence, the patient died in the eighth week subsequent to double parotitis.
5	Chvostek	Med. Chirurg. Rundschau, June, 1864, p. 188.	1	Blood infect'n; liver abscess.	Laryngeal perichondritis; deep jaundice; abscess of lung; pneumothorax	Died.	Two large abscesses in liver, evidently pyæmic and secondary; also abscess in left lung.	

6	Burder	Lancet, Oct. 17, 1874.	1	Blood infect'n; liver abscess.	Icterus on sixth day of fever in a boy nine years of age; greatly increased after a chill on the eighth day; liver dulness normal; diarrhœa.	Died.	The liver was a mass of small abscesses; superficial ulceration of Peyer's patches.	Had the bath treatment; death on seventeenth day of the disease.
7	Heitler	Wien. med. Presse, 1875, No. 3.	1	Blood infect'n; parenchymatous change in liver.	Date of beginning of fever uncertain; jaundice probably about third week, preceding diarrhœa; stools bilious, subsequently yellow; no chills; urine albuminous, also blood and tube-casts in it; normal liver percussion; increasing jaundice; delirium; coma.	Died.	Ulcers in ileum; lungs congested; liver rather large, flabby, soft; brown bile in gall-bladder; spleen enlarged to four times its normal size.	
8	Sidlo	Der militär Arzt, Wien, 1875, No. 23, p. 20.	1	Abscess of liver.	Pain in the hepatic region on thirty-second day of typhoid fever; on thirty-fifth day jaundice; swelling of liver; abscesses over right mastoid, in right temple, and in right axilla; tumor there gradually shrank; great emaciation; gradual diminution of liver dulness and of jaundice.	Recov.	.....	Abscess of liver discharged through bowel. pus and blood passing by the bowel on eighty-fourth day, after severe abdominal pain; complete recovery by one hundred and twentieth day.
9	Griesinger	Infectionskrankheiten; detailed also by Hagenmüller, Thèses de Paris. 1876, No. 269.	1	Cholecystitis with probable cholangitis.	Woman, aged twenty, in sixth week of typhoid fever. peritonitis, icterus, chills; painful tumor to right of umbilicus; swelling of liver; great prostration; convalescence. In eighth week return of tumor, with chills, icterus, vomiting; got better; subsequently two more relapses; the symptoms disappearing under treatment with large doses of opium. Final recovery in fifth month.	Recov.	.....	The patient had previously had jaundice several times, especially at her periods. The case is remarkable for its length, the recurrence of the symptoms, and the final recovery.
10	Laveran	Case communicated to Hagenmüller and published by him, Thèses de Paris, 1876, No. 269.	1	Cholecystitis.	Repeated bilious vomiting, severe pain in right hypochondrium, which is painful; icterus slight; fever reaching 40.6° C.; considerable prostration; no tumor mentioned.	Recov.	....	Symptoms came on in sixth week, early in convalescence.
11	Goltdammer	Deutsch. Arch. f. k. Med., 1877, vol. xx. p. 68.	2	First case most likely from blood infection and parenchymatous change Second, catarrhal; but not fully enough reported to be certain.	Tenderness and swelling in hepatic region in one case of severe typhoid fever; no details given of second case except that the jaundice was of short duration and occurred in convalescence.	Recov.	.....	Very meagre details given. In both cases the bath treatment had been employed.

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12	Murchison	Diseases of the Liver, 2d ed., 1877, Cases CXXXVII., CXXXIX. Two mentioned (p. 401) without being described. One case (under Rostan's care) communicated (CXXXVIII.).	5	One catarrhal (CXXXVII.); one blood infection (CXXXIX.); in the other two blood infection & parenchymatous changes; in the communicated case this also most likely cause.	In first case clay-colored stools; no hepatic tenderness; constipation; jaundice occurred in a relapse; case recovered. In Case CXXXIX. jaundice appeared on fourteenth day associated with albuminuria, subsequent thrombosis, jaundice passed away; death from gradual exhausion. In two cases no particulars. In communicated case jaundice persisted during convalescence.	3 died. 2 recov.	In two cases liver found to be small, and its secreting cells loaded with oil.	
13	Petrina	Prag. med. Wochen., 1881, Nos. 41–43.	4	Case I. Blood infection, pylephlebitis with thrombi, miliary abscesses in liver.	Severe typhoid case; jaundice appeared thirteenth or fourteenth day of disease, not preceded by chill, and gradually increased, becoming very deep; fever high (highest 40.6° C.), with marked morning remissions and evening exacerbations; profuse sweating; moderate meteorism; liver enlarged and sensitive, left lobe especially; stools yellowish-brown or brown; profuse diarrhœa toward end; bile-pigment but no albumin or sugar in urine.	3 died. 1 recov.	Fresh and old cicatrizing lesions in Peyer's patches; lungs congested; liver very large, full of yellow points, which are found to be miliary abscesses; granular and fatty changes in hepatic cells; thrombosis of some of the finer portal veins; dark bile in gall-bladder; spleen large; in pancreas a few yellow foci; lungs congested.	
				Case II. Blood infection, probable parenchymatous change in liver.	Icterus eighteenth day of disease; repeated chills; marked fluctuation between morning and evening temperature; liver enlarged; whole region sensitive; vomiting and epigastric pain; profuse sweats; no albumin in urine; ascites; congested lungs, œdema of lungs.	.....	.....	No autopsy. The marked gastric symptoms and the occurrence of ascites are remarkable features of this case, which was probably one of pylephlebitis.
				Case III Probable parenchymatous change.	Jaundice on fifteenth day, preceded by chill on thirteenth; abdomen sensitive, especially liver region over left lobe; liver increased in size; urine contains bile-pigment, no albumin; chills recur. Patient left the hospital improving, but still jaundiced; the liver and spleen were still swollen after nearly four weeks.	.....	.....	Though not specifically stated, it is likely that this patient recovered.

				Case IV. Cholecystitis, with cholangitis; interstitial hepatitis.	Jaundice on second day of a typhoid fever relapse; jaundice preceded by chills; liver enlarges, becomes tender on pressure; bilious stools, subsequently yellow; repeated chills; apparent recovery, except slight jaundice and enlarged liver remaining. Returns to hospital, a little over a month after leaving it, with œdema of lower extremities; yellowish, liquid stools; urine full of bile-pigment; general dropsy develops, with hydrothorax and ascites, and abdomen is tapped; dies of œdema of the lung after a lingering illness.	.....	Cicatrized Peyer's patches; thickening of mucous coat of gall-bladder; peritoneal adhesions between stomach and liver; liver small, surface granular; biliary ducts in liver filled with brownish-yellow masses, some containing spear-shaped concretions, others fibrinous coagula; some of the smaller bile-ducts have undergone obliteration with increase of connective tissue; this process also spread to Glisson's capsule, and led to atrophy of the liver; thus interstitial hepatitis had occurred following inflammation of gall-bladder and bile-ducts; cholelithiasis accedens is also recorded.	
14	Sabourin	Revue de Méd., 1882, p. 600.	1	Parenchymatous change (acute yellow atrophy).	Man, twenty-nine years of age; deep jaundice preceded by epistaxis; time of appearance of jaundice uncertain; meteorism, diarrhœa, delirium, albuminous urine, intestinal hemorrhage; average temperature 39° to 40.6° C.; pain on pressure in right iliac fossa and right hypochondrium.	Died.	In intestines ordinary typhoid fever lesions; heavy congestion of lungs; liver diminished in size in a state of acute atrophy with fatty degeneration of the hepatic cells; gall-bladder contained a small amount of almost healthy-looking bile.	
15	Stedman	Med. and Surg. Rep., Boston City Hospital, 3d ser., 1882.	1	Parenchymatous change in liver.	Jaundice, probably early in second week; tenderness in right hypochondrium; no epistaxis, nausea, or vomiting; urine, besides bile-pigment, contains a trace of albumin; diarrhœa, hypostatic congestion of lungs; highest temperature recorded 102°.	Died.	Liver enlarged and of nutmeg appearance: Peyer's patches swollen, not ulcerated; spleen softer but small; kidneys enlarged and in a state of cloudy swelling.	This case is not free from doubt as one of typhoid fever. Death occurred on the eighteenth day, and Peyer's patches should then have shown ulceration.
16	Freundlich	Deutsch. Arch f. klin. Med., 1883, Bd. xxxiii. p. 318.	1	Blood infect'n; pyæmia.	Jaundice early in fifth week of typhoid fever, in which thrombosis of the scrotal veins followed by gangrene there and in the inguinal region had arisen; repeated chills; in the progress of the case persistent albuminuria and intestinal hemorrhages.	Died.	Anatomical lesions of enteric fever in intestines; double croupous pneumonia of lower lobes; condition of liver not stated.	Death in middle of fifth week.
17	Mathieu	Revue de Méd., July, 1886, vol. vi. p. 633.	...	.....	.....	.....	....	Very doubtful case, in which at end of the second week temperature became 38° C. Was it abortive typhoid followed by a relapse?

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18	Sorel	Bull. et Mém. de la Soc. Méd. des Hôpit. de Paris. 1889, vol. vi. 3d ser., p. 224.	6	Cannot judge from slight description.	Four cases happened at beginning of the malady, two of which were fatal; one case jaundice shortly before death; one in convalescence. In one case, p. 239, epistaxis was frequent.	3 died. 3 recov.	.....	No particulars given, except that in one case in which there had been also bloody urine, the liver was said to have been altered.
19	Romberg	Berlin. klin. Wochenschrift, March, 1890.	1	Blood infect'n; thrombosis of vena porta, and small liver abscesses.	Intestinal hemorrhage; albuminous urine; chill on twenty-fourth day of the disease; next day jaundice; brownish or yellow soft stools, sensitive abdomen, increased liver dulness and tenderness in hepatic region; fever with irregular remissions; icterus became intense; repeated chills. Death on thirty-first day of disease.	Died.	Many typhoid ulcers, for the most part in the process of healing; phlegmonous suppuration in mesentery near cæcum; thrombi in ileocæcal vein and its branches; liver markedly enlarged and full of small abscesses, especially of left lobe; masses of staphylococci in thrombi in portal veins.	
20	McPhedran	Canadian Practitioner, March, 1891.	1	Blood infection and parenchymatous change (diffuse pylephlebitis).	Symptoms came on, in a man, as convalescence was about to set in; temperature became irregular; recurring chills with sweating; jaundice; increase of liver dulness. Subsequently signs of chronic peritonitis.	Died.	At autopsy, diffuse pylephlebitis and chronic purulent peritonitis found; in the mesentery a small abscess apparently originating in a mesenteric gland.	
21	Jamieson	Imperial Maritime Customs, China Med. Reports, 1888–95, 37th issue, pp. 63, 67.	9	Blood infection with probable parenchymatous change.	Jaundice appeared in one case on the fifth day, in one on the eighth, in three on the tenth, and one respectively on the eleventh, fourteenth, seventeenth, and forty-fourth days; deep jaundice in all, and symptom not of gradual onset.	4 died. 5 recov.	.....	Four of the five cases in which jaundice appeared before the eleventh day proved fatal. Severe intestinal hemorrhage occurred in three of the fatal cases.
22	Lannois	Rev. de Méd., 1895, p. 911.	1	Parenchymatous change; cholecystitis.	Icterus began toward third week of severe typhoid fever; at first light, it became very intense, black; liver greatly enlarged, marked meteorism, intense pulmonary congestion. Death eleven days after appearance of icterus; not long before, a superficial abscess appeared on back of hand, and one on the internal surface of the leg on the same side.	Died.	Many Peyer's patches involved. Enormous liver, weighing 3000 grammes, yellow and fatty; gall-bladder greatly distended, containing, besides a clear liquid, flocculent muco-pus; superficial erosions in membrane; biliary passages, no ulceration or abscesses.	This was a very marked case of suppurative cholecystitis.

23	Osler	Transactions of Association of American Physicians, 1897.	2	Catarrhal in first case; blood infection (with parenchymatous change?) in second.	In the first case nausea and vomiting came on early in a relapse of typhoid fever, of which the original attack was one of moderate severity; jaundice appeared fourth day of relapse; no enlargement of liver; tenderness on deep pressure in front of tenth rib; nausea and vomiting prominent symptoms; profuse sweats; clay-colored stools; temperature range from 102° to 103.5°. In second case severe attack of typhoid fever; jaundice at end of second week; jaundice became of considerable intensity; meteorism; abdomen not tender; liver dulness not decreased; marked delirium; nystagmus; temperature, which had been high (105°), dropped to 97.2°.	1 recov. 1 died	.....	In the second case the patient died on the sixteenth day. It was remarkable that, notwithstanding a falling temperature for four days, the pulse was of good volume.
24	Da Costa	Present paper.	5	1 catarrhal; 1 pylephlebitis; 3 parenchymatous changes in liver with blood infect'n.	Detailed in present paper. Jaundice marked in all.	3 died. 2 recov.	....	All were severe cases of typhoid fever.

out a consideration of the character of these complications. Of the relative importance of these, we may get a fair idea by examining Hölscher's statistics in 2000 fatal cases of typhoid fever at the Pathological Institute of Munich.[1] Among 227 involving the liver and gall-bladder, there were 203 of disease of the liver structure; 12 cases of abscess; 3 of acute yellow atrophy; 1 of amyloid degeneration of the liver; 5 of diphtheritic processes in the gall-bladder and suppuration, including one of perforation of the gall-bladder; 3 of œdema of the gall-bladder; while 22 in addition are classed simply as icterus, without being linked to any organic disease.

The ordinary parenchymatous alterations, that are presumably represented by the 203 in the numbers just quoted, are not to be recognized during life, and force themselves on our attention only in the few instances in which they are attended with jaundice; the very great majority of the changes in the liver structure in typhoid fever give rise, indeed, to no symptoms. Leaving for separate consideration diseases of the gall-bladder, *abscess* of the liver is the affection which most often manifests itself. Yet it cannot be said that abscess of the liver in typhoid is often met with. Hölscher's statistics have just been quoted. Romberg mentions 677 cases with 88 deaths, among which there was but one liver abscess; it was associated with suppurative pylephlebitis. Schultz[2] analyzed 3686 cases with 362 deaths, without a single instance of hepatic abscess.

As regards abscess of the liver, I have collected twenty-two cases in which the association with typhoid fever seemed beyond doubt, and which admit of more or less complete clinical analysis. Others that have been reported I have rejected as very uncertain, as the combination with typhoid fever is not proved. Bouillaud's case, mentioned by Andral,[3] which has been questioned, I have included. Of the 22 cases, 7 only had jaundice; in 3 it is specifically mentioned as not present, and in 12 it is not mentioned at all, making 15 cases out of 22 in which jaundice may be fairly presumed to have been absent. Thus jaundice is not a symptom to be depended on in the diagnosis of abscess of the liver in typhoid fever. More important are chills, violent, prolonged, and repeated, as in Barth's[4] case, and generally preceding the jaundice, should this happen, as in Romberg's case; great variations in temperature, as in Case I. of Petrina; profuse sweating and sensitiveness in the region

[1] Münchener med. Wochenschrift, January, 1891, Nos. 3 and 4.
[2] Observations made at the Hamburg Hospital, quoted by Romberg, loc. cit.
[3] Clinique Méd., 3d edition, 1834, vol. i. p. 616.
[4] Bull. de la Soc. Anat., 1853, p. 80.

of the liver. The liver may or may not be swollen; in Goltdammer's case it was swollen. In Gerhard's[1] case the right hypochondrium was prominent, and tender on pressure, and fluctuation was detected over the right lobe of the liver. As further symptoms pointing to abscess of the liver, should there be any hepatic manifestations, are abscesses in other parts of the body, as in the parotid (Louis's case), in the perichondrium of the larynx (Chvostek's case), over the mastoid region (Sidlo's case). At times hepatic symptoms are wholly wanting, and the abscess is only found at the autopsy.

All the symptoms mentioned may also happen in pylephlebitis, except the rarest, fluctuation; especially the repeated chills, the pain and tenderness in the hepatic region, the high irregular temperature; and I know no way of distinguishing pylephlebitis from abscess, with which, indeed, it is generally classed, unless by the progress of the case, in which enlargement of the subcutaneous abdominal veins and collections of fluid in the peritoneum may be observed in addition. But the latter signs occur to a decided extent only where there is also marked thrombosis in the portal veins or its main branches, as in a case of Lannois,[2] and there is apt to be painful enlargement of the spleen as well as of the liver. I think jaundice, most probably pyæmic and from infected thrombi, is apt to happen among the symptoms of pylephlebitis with greater frequency than in abscess of the liver not associated with this, and to become deeper; but it is far from invariable. It was absent in the case of Asch and of Bernhard,[3] an instance of pylephlebitis from suppurating glands in the mesentery, and where there was a purulent thrombosis of the mesenteric veins and the venæ portæ were full of pus.

Viewed in its clinical bearings, we find abscess of the liver in typhoid fever under these conditions: as metastatic abscess, due to a pyæmic infection from other parts of the body, as the consequence of pylephlebitis, which is nearly always caused by an infection from typhoid lesions in the intestine, or from suppurating mesenteric glands and a resulting infective thrombosis; or, as owing to typhoid ulceration in the biliary passages and secondary suppuration. The first of these causes is illustrated by most of the cases in the table, notably by those of Louis, of Chvostek, of Sidlo, of Dunin,[4] of Barth.[5] To the second category belong the cases of Lannois, of Osler, of Romberg, of Gerhard,[6] of

[1] Medical News, July 24, 1886.
[2] Revue de Médecine, 1895, p. 918.
[3] Berlin. klin. Wochenschrift, 1882, xiv. p. 772, and Jahrb. für Kinderheilkunde, N. F., 1886, Bd. xxv.
[4] Deutsch. Arch. f. k. Med., 1886, Bd. xxxix. p. 379.
[5] Bullet. de la Société Anat., 1853, p. 80.
[6] Loc. cit.

Tüngel,[1] in which pus from a suppurating lymphatic gland near the cæcum broke into a root of the superior mesenteric vein; of Bückling[2] with a similar history; of Asch and Bernhard,[3] where there was also a suppurating mesenteric gland. Cases belonging to the third group are the rarest. A very striking one is mentioned by Klebs,[4] in which a suppurative inflammation of the bile passages within the liver happened, and their dilatation formed abscesses filled with thick, greenish, muco-purulent liquid. In the pus from liver abscesses, typhoid fever bacilli were found by Lannois. It may be also a question whether in some of the cases regarded as metastatic there have not been separate foci of inflammation and suppuration due to the typhoid bacilli; for instance, in the cases in which the parotid glands, as well as the liver, have been implicated.

In this connection we may discuss whether there be a form of typhoid fever in which liver symptoms arise, including jaundice, owing to the direct action of the specific micro-organisms on the liver or the bile channels. Mathieu[5] describes, under the title of "typhus hépatique benin," a case which he believes to have been of this character, and in which a relapse similar to a typhoid fever relapse happened, and Pfuhl[6] cites nine cases that came on after swimming repeatedly in a swimming school in the infected Elbe water at Altona near Hamburg, and all of which had fever and jaundice. I have analyzed these cases, and do not find their clinical history closely corresponding to typhoid fever. They all recovered, and are spoken of as due to mixed infection. Mathieu's case also recovered; and, as these cases happened before the introduction of the Widal test, we must remain in doubt as to their nature. I had at the Pennsylvania Hospital last year a case of jaundice in a colored woman (Case No. 2775), with fever, violent epistaxis, hebetude, diarrhœa, and albuminous urine, in which the Widal test gave positive reactions. She had been suffering with fever for two weeks, and it preceded the jaundice. The case proved fatal in the third week of the disease, and seemed to be an undoubted one of typhoid fever with hepatic complication. At the autopsy no lesion was found in the intestinal glands. The mesenteric glands were here and there enlarged, and one appeared as if it had pressed upon the choledoch duct; the gall-bladder was much distended, and its mucous coat inflamed; the liver was small and in a high state of fatty degen-

[1] Thierfelder, Ziemssen's Handb., Bd. viii. p. 84.
[2] 36 Fälle von Leberabscess, Berlin, 1868.
[3] Loc. cit.
[4] Handbuch der pathol. Anat.
[5] Revue de Méd., July, 1886.
[6] Deutsch. milit. arztl. Zeitsch., 1898, vol. xvii. pp. 9, 10.

eration; the spleen was small; the kidneys large, with signs of interstitial nephritis. Unfortunately, through a misunderstanding, no cultures were made from the liver and gall-bladder, as had been intended, and, notwithstanding the positive character of the Widal test, I hesitate greatly to bring forward the case as one of hepatic typhoid without intestinal lesion; it may have been one of acute yellow atrophy, of which it presented also many of the symptoms.

More common in typhoid fever than diseases of the liver itself are the diseases of the bile passages. We know through recent researches how frequent is their infection, especially the gall-bladder infection, with the typhoid bacilli. Chiari[1] reports the results of autopsies in twenty-two patients, and only in three was the bacillus absent from the gall-bladder. In twelve cases there was inflammation of the mucosa alone; in one the whole wall was affected, causing peritonitis.[2] In the discussion that followed a valuable paper by Mason,[3] on "Gall-bladder Infection in Typhoid Fever," Councilman stated that he had found the typhoid bacillus in nearly every case. Gilbert and Girode[4] demonstrated the presence of the typhoid bacillus in suppurative cholecystitis. Dupré[5] got pure cultures of typhoid bacilli from the gall-bladder of a patient operated on for gallstones six months after typhoid fever; in another case, in a man who died about the fifteenth day of typhoid fever, although the gall-bladder presented no obvious pathological changes, pure cultures of Eberth's bacillus were obtained.

Not only do these gall-bladder infections happen in the course of typhoid fever in association with the characteristic intestinal lesions of the disease, but they have been observed when these were absent. Cases of the kind are reported by Guarnieri[6] and in most interesting papers by Osler[7] and by Cushing.[8] Mark Richardson's[9] case, in which there was no distinct history of typhoid fever, but in which the typhoid bacillus was found in the fluid obtained from the distended gall-bladder by operation, is another case in point. It is quite as likely that the infection of the gall-bladder occurs in these instances through the typhoid bacilli in the blood as by direct infection from the continuous intestine. Further, great interest is attached to these gall-bladder infections in typhoid

[1] Eleventh Intern. Med. Congress, Zeitschr. f. Heilkunde, 1894, Bd. xv. S. 199.
[2] Case described, Prager med. Wochenschrift, 1893, No. 22.
[3] Transactions Assoc. American Physicians, 1897.
[4] Mém. de la Soc. de Biologie, 1890 and 1893.
[5] Infections Biliaires, 1891.
[6] Contrib. alla patog. della infez. biliari.; also, Baumgarten's Jahresbericht, 1892, S. 234.
[7] Trans. Assoc. American Physicians, 1897.
[8] Bulletin of the Johns Hopkins Hospital, vol. ix. No. 86.
[9] Boston Medical and Surgical Journal, December 16, 1897.

fever from the now established fact that they lead to the formation of gallstones; as, on the other hand, gallstones seem to invite the bacillary infection to the gall-bladder. The association with gallstones is curiously illustrated in a case by Chantemesse,[1] in which living typhoid bacilli were found in a gallstone removed by operation eight months after an attack of typhoid fever. Van Dungern's[2] case of bacilli found fourteen years and a half after typhoid fever in the pus from an abscess formed around the gall-bladder is unique; here, however, no stones were detected. The patient recovered.

Now, from the frequency, it might almost be said constancy, with which infection of the gall-bladder happens in typhoid fever, it would be supposed that symptoms referable to it are very common. But it is just the reverse. In the cases of irritation or the lighter cases of inflammation produced by it, there are absolutely no symptoms; even in the more severe cases, in which obvious lesions are found, symptoms are often absent or, at least, not recognizable; and thus the majority of cases pass undiscovered and mostly unsuspected. It is only the very marked ones, and chiefly those in which perforation has happened, that have been noticed. I shall attempt an analysis of such of the cases as have been published with sufficient fulness to give real information, and which seemed to me to be undoubtedly linked to typhoid fever, for it is astonishing in how many instances the evidence concerning this is most meagre. I have been greatly aided in the task by the courteous permission of Dr. Westcott to make use of the references he had prepared for the remarkable work of Dr. Keen, *On the Surgical Complications and Sequelæ of Typhoid Fever*, and by the most efficient assistance of Dr. Woodbury. After rejecting all the doubtful cases, I got together and tabulated fifty-three cases of cholecystitis in typhoid fever, some simple though marked, some suppurative, some perforative. But before analyzing these, it may be well to inquire in what proportion these affections have been noticed by pathologists irrespective of, as well as with, typhoid fever. Courvoisier[3] gives us valuable information on this point. Of 16 cases of cholecystitis of catarrhal origin or with beginning suppuration, fully 5 occurred in the course of typhoid fever. Six cases out of 55 of empyema of the gall-bladder were due to infection, one of which was from typhoid; 41 were due to cholelithiasis. In 7 cases of phlegmonous infiltration of the walls of the gall-bladder, typhoid was twice the cause, and the other 5

[1] Traité de Méd., tome i. p. 764.
[2] Münch. med. Wochenschrift, 1897, No. 26.
[3] Casuist. Statistische Beiträge z. Path. u. Chir. der Gallenwege, Leipzig, 1890, pp. 76–94.

cases were due to cholelithiasis. Fatal result is the rule in purulent cholecystitis. Of 82 cases, 53 proved fatal. Among these were 10 cases due to typhoid. In many of the cases there was no suspicion of cholecystitis prior to the autopsy. In cases of perforation of the gall-bladder, with encapsulation into the abdominal cavity, mentioned by Courvoisier, there were four in which no calculi existed, and which were due to typhoid.

Cholecystitis in typhoid fever, when at all marked, is a grave complication, no matter what be its exact form. In 58 cases of typhoid cholecystitis I have collected, there were 39 deaths and 15 recoveries, while in 4 the result was uncertain or not stated. Of the different forms, the instances of perforation without operation are the most fatal; 1 only out of 24 recovered by a discharge through the abdominal walls (case of Salzman); 3 recovered after operation (cases of Alexieef, Williams and Shield, Osler and Halsted). In suppurative cholecystitis there are a number of recoveries, but also as the result of operation (cases of Caspersohn, Mason, Richardson, Williams and Shield, Osler and Halsted). In the cases of cholecystitis which are catarrhal, recovery is not infrequent; where there is also cholangitis (as in Case IV. of Petrina and in Sander's case), the prognosis is not good. But Griesinger's case, in which this complication probably existed, recovered.

To proceed now with the clinical analysis of the 53 cases I have collected, to which, for some purposes, I shall add the 5 of cholecystitis with jaundice detailed in the table printed in this paper. Of these 58 cases there were 22 in which perforation of the gall-bladder happened. In 6 of the 22 cases of perforation gallstones were found, while in 16 they are either stated to be absent or are not mentioned; thus gallstones were not encountered in more than about one-fourth of the cases of perforation. Suppurative cholecystitis may, from the descriptions, be recognized in 24 of the 58 cases; and in eight of these there was also perforation. In the other instances the lesion was catarrhal, with very slight if any suppurative change. Ulcers of the gall-bladder cannot be absolutely separated from suppurative cholangitis, as in nearly all instances some suppuration coexists.

As regards *sex*, there is very little difference in the occurrence of the marked gall-bladder complications of typhoid fever. In 48 cases in which the sex is mentioned 26 were males, 22 females. The affections may be met with at almost any *age*. In 48 cases 8 were twelve years of age or less; 40 cases were over twelve years of age. The youngest

case happened in a girl, aged five years (case of Alexieef[1]); the oldest in a man, aged sixty-seven years (case of Anderson[2]).

The question of the *diagnosis* of these gall-bladder complications, and the possibility of telling them apart, is of great importance. It has been stated already that in many instances they are latent, and have only been discovered after death. But the knowledge of their occurrence, and the search for them in acute cases, will cause them to elude discovery less and less frequently. The marked symptoms are pain and tumor.

Pain is almost never absent. It is epigastric, or in the right hypochondrium, and is very often referred directly to the seat of the gall-bladder. It may be so severe that the patient shrieks, especially when he moves (as in Budd's case), or rolls in agony (Barthez and Rilliet's case). It often occurs in severe paroxysms. In the great majority of instances it is associated with marked tenderness, which, however, is not apt to remain confined to the region of the gall-bladder, but to be found also over the whole of the right hypochondrium or right side of the abdomen; and the entire abdomen even may be sensitive, most likely then from a spreading peritonitis. On the other hand, the general tenderness may become localized in the region of the gall-bladder. In a few instances sensitiveness, without pain, is spoken of; in a very few, as in a case of Louis', pain is mentioned as absent. Rigidity of the abdominal walls, especially on the right side, not infrequently coexists.

Tumor is of diagnostic significance as great as or even greater than pain, though it is not so common a symptom. It is specially mentioned in 21 out of 53 cases, only, therefore, in less than one-half. But it is probably present in larger proportion; the typhoid state of the patient and the marked meteorism that generally exists prevent its detection. It occupies the seat of the gall-bladder, and is thus to be looked for at Mayo Robson's[3] point, namely, at the junction of the upper two-thirds with the lower third of a line drawn from the ninth rib to the umbilicus. In a number of instances it is described as pear-shaped and firm, also as being tender on pressure; it may be a mere resisting mass below the costal margin. The tumor of the gall-bladder may be noticed to disappear slowly, or, where perforation happens, the disappearance may be sudden. In some instances the tumor swells up from time to time, as in the remarkable case of Leudet,[4] in

[1] Journ. Dietskaya Med, 1896, No. 4; abstracted in the American Journal of the Medical Sciences, October, 1897, p. 466.
[2] Medical News, August, 1896.
[3] Diseases of the Gall-bladder and Bile-ducts, 1897, p. 87.
[4] Clinique Médicale de l'Hôtel Dieu de Rouen, 1874.

which a woman who left the hospital apparently well, though with signs of a tumor from typhoid cholecystitis still perceptible under the false ribs, had markedly recurring swelling with tenderness at each menstrual period for six months. The tumor that is found, though having its origin in the lesion in the gall-bladder, may not be due to this viscus, strictly speaking, but, in the perforated cases, be a pus-cavity formed around it. The history of the case and the irregular shape of the swelling may lead us to suspect its cause, but there is no certainty in the discrimination.

Among the less marked symptoms are jaundice, nausea and vomiting, and chills. *Jaundice* occurred in 17 out of 58 cases, was thus absent or not mentioned in 41, and only occurs, therefore, in less than one-third of the cases. It is not, as a rule, deep, though, after it shows itself, it persists. It does not occur in the cases with perforation in any greater proportion; 5 only out of the 23 cases of perforation had jaundice. Nor is it of much more frequency in the suppurative cases, the proportion being 6 out of 24. Indeed, its relation to the gall-bladder lesions in typhoid fever is uncertain and of little value in diagnosis. In rare instances the jaundice is due to impaction of a gallstone, as in the case of Barbe,[1] in which attacks of gallstone colic and steadily deepening chronic jaundice preceded typhoid fever; and, at the autopsy, besides the characteristic intestinal lesions, a perforated gall-bladder was found and an obstruction of the common choledoch duct by a stone.

Nausea and *vomiting* occur as transient symptoms, though in much greater frequency than in the ordinary course of typhoid fever. They are mostly to be noticed at the beginning of the gall-bladder complication. In Legendre's[2] case the vomiting of large quantities of green, bitter fluid is specially mentioned. *Chills* are conspicuously absent. I find their occurrence noted in only 3 out of 54 cases, including the cases in which perforation happened. Burger's[3] case began with a severe chill; chills happened six days before death in Budd's[4] case, and happened also in one of Osler's cases. The other symptoms are those of severe cases of typhoid fever. But the frequent occurrence of pulmonary complications, especially toward the end of the fatal cases, is noteworthy. In a number of instances pneumonia was the immediate cause of death.

As regards the diagnosis of typhoid cholecystitis, this is impossible

[1] La France Méd., 1884, ii. p. 1071.
[2] Bull. de la Société Anatom. de Paris, 1881, p. 1893.
[3] Deutsch. Arch. f. k. Med., 1873, p. 623. [4] On Diseases of the Liver, 3d ed., 1857, p. 196.

with any certainty, except where tumor is present, though it may be suspected if there be nausea and vomiting, a sense of weight, and sensitiveness over the gall-bladder. But the occurrence of tumor and of pain and tenderness at or near the seat of the gall-bladder make the diagnosis not difficult. The most likely error is confounding the malady with an appendicitis. As a rule, the seat of pain and tenderness and swelling is different; in the one case in the right iliac fossa, in the other in the region of the gall-bladder. But we cannot trust implicitly to this; as in appendicitis, especially at its upper part, or where the appendix is not normally situated, the localization of the symptoms may be high up; and in cholecystitis the pain and tenderness may not be most marked over the gall-bladder, and the swelling may be very difficult to define.

An exact discrimination of the different forms of typhoid cholecystitis cannot be always made. They are all most likely to come on late in the disease, or after convalescence has been established, and all, whether with or without perforation, as Hagenmüller[1] has clearly established, are prone to be associated with local peritonitis in the neighborhood of the gall-bladder. Where there are abscesses in other parts of the body, and we can exclude pylephlebitis and hepatic abscess, a *suppurative cholecystitis* may be inferred, if pain and tumor be present. If there be a history of biliary colic and gallstone, or if this arise in the progress of typhoid fever or not long subsequent to it, signs of cholecystitis mean suppurative cholecystitis. I think, too, though there are not many observations on this point, that examinations of the blood will help us materially. We know through the researches of Thayer[2] that in typhoid fever the number of white blood-corpuscles varies but little from the normal standard, about 6000 per c.cm. Marked leucocytosis, if there be symptoms of cholecystitis, points to its being suppurative, as in Mason's case and in Anderson's case, where there was perforation. On the other hand, in a case of Osler's that recovered, there was no leucocytosis, and we may infer the cholecystitis not to have been purulent. In laying stress on leucocytosis we must, however, exclude abscess of the liver, in which condition it may also exist. Yet here the local symptoms are different: there is less pain, no tumor over the gall-bladder, and in doubtful cases I should attach much importance to the occurrence of chills. The analysis in this paper has proved their extreme rarity in cholecystitis of any form, whereas they are very com-

[1] De la Cholecystite dans la Fièvre typhoïde. Thèses de Paris, 1876, No. 269.
[2] Johns Hopkins Hospital Reports, vol. iv.

mon in abscess and in pylephlebitis, as is sweating. In none of these conditions can we lay much stress on the presence or absence of jaundice. There are cases of gall-bladder affection in typhoid fever in which there is mere distention with bile or a watery fluid. Case IV. of this paper probably belongs to these. They have been supposed, as in the case of Dumoulin,[1] to be due to retention of bile owing to nervous disturbance attending the fever, analogous to the retention of urine; or they may be the result of obliteration of the cystic duct, as in a case of Louis,[2] where the bile in the distended gall-bladder had the appearance of urine, and the cystic duct was compressed by an enlarged lymphatic gland that surrounded it. No means exist of distinguishing these cases during life from acute cholecystitis, except it be by the absence of severe pain and very marked tenderness. Then it is likely that they are really instances of bacillary infection of the gall-bladder, and that the typhoid bacilli will be found in the fluid, only marked inflammation has not been induced.

Perforation of the gall-bladder has as its chief symptoms suddenly developed or intensified pain, collapse, and peritonitis. In some instances that have been reported there is also marked drop of temperature, as in the cases of Bonamy[3] and of Bond.[4] The effect on the tumor is often a decided lessening or a disappearance. Peritonitis, which may remain local, as in the case of Hawkins[5] and others, develops, and may lead to encapsulation of the discharged contents of the gall-bladder. On the other hand, a subsequent general peritonitis may occur. The course is often a comparatively slow one, two of the reported cases, Ranvier's[6] and Archambault's,[7] not dying until the twelfth day after the perforation.

It is evident how very similar the symptoms are to those of intestinal perforation. Gall-bladder perforation can be, indeed, distinguished only by the seat of the pain and the previous existence of the tumor. Should jaundice be present it would be an additional aid in discrimination. On the other hand, intestinal hemorrhages preceding the symptoms of perforation, and rapidly developing general peritonitis, belong more strictly to the intestinal lesion; local peritonitis in the upper part of the abdomen on the right side is more characteristic of gall-bladder perforation, as is a slower progress of the symptoms. Fall of temperature, too, attending the collapse, occurs much oftener in intestinal perforation in typhoid fever than in gall-bladder perforation in the same disease.

[1] Gaz. Méd. de Paris, 1848, p. 551.
[2] Fièvre Typhoïde, vol. i. p. 201.
[3] Gaz. Méd. de Nantes, 1890, p. 133.
[4] British Med. Journ., July 12, 1884, p. 67.
[5] Medico-Chir. Trans., vol. lxxx. p. 138.
[6] Bull. de la Soc. Anat., 1864, p. 433.
[7] Bull. de la Soc. Anat., 1852, p. 90.

The *treatment* of the jaundice attending these different hepatic affections will be guided by our recognition of the probable cause. Those which are due to blood infection and to the finer parenchymatous changes in the liver cannot be reached by any special treatment, which must be that of the grave underlying typhoid condition. I will, however, point out that two of my cases recovered while taking decided doses of mineral acids, and this was also the result in two of Murchison's cases. In abscess of the liver, as well as in pylephlebitis, large doses of quinine may be employed. In the ordinary form of cholecystitis, recovery has followed applications of leeches over the swelling, followed by poultices, as in Observation No. LXVIII. of Frerichs. Besides the general treatment of the typhoid state, attention must be paid to the character of the discharges from the bowels; when very dark and showing vitiated bile, small doses of mercurials should be given. Leudet's[1] case got well under calomel and under frictions with belladonna. The suppurative cases require support, and, as soon as we are reasonably sure of their character, surgical interference, the admirable outcome of which was seen in the cases of Caspersohn,[2] of Williams and Shield,[3] of Alexieef,[4] of Mason,[5] of Osler and Halsted,[6] of Mark and Maurice H. Richardson.[7] Among the perforation cases I know of only one recovery without operation, the case of Salzmann,[8] in which a discharge occurred through the abdominal wall. An operation alone promises success, and how well it may succeed is proved by the results of Williams and Shield and one of the cases of Osler and Halsted.

[1] Loc. cit.

[2] Festschr. f. Fr. von Esmarch, 1893, p. 455, Kiel and Leipzig.

[3] Lancet, March 2, 1896.

[4] Journ. Dietskaya Med., 1896, No. 4. Quoted in The American Journal of the Medical Sciences, October 1897, p. 466.

[5] Trans. Assoc. American Physicians, 1897.

[6] Ibid.

[7] Boston Med. and Surg. Journ., December, 1897.

[8] Med. Corresp. Würtemb. Arztl. Verein., 1870, xl. 84.

A NEW PATHOGENIC CHROMOGENIC BACILLUS.

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The bacillus about to be described came from some rags obtained at a paper-mill located about twenty miles west of Boston. The sample from which it was isolated was taken from the bottom of a pile which had been in the mill-yard for several months, and which had been condemned by the local Board of Health as a nuisance. Attention was called to the organism by the green color produced in tubes of nutrient bouillon in which the sample had been placed. A guinea-pig which had been inoculated with about one cubic centimetre of a bouillon culture died within forty-eight hours, and the cultures taken from the heart's blood and from various organs showed, the next day, a distinct green color. Plates were made from these tubes, the organism isolated in pure culture, and studied with the following results.

Morphology. The bacillus is short and stout, with rounded ends, from 0.9 μ to 2.8 μ in length and 0.4 μ to 0.9 μ in diameter; it is frequently united in pairs, but never in chains of more than two elements. Its length seems to depend somewhat upon the culture medium on which it is grown; short forms, in which the length does not exceed the breadth (0.9 μ), and which might easily be mistaken for micrococci, are most common on agar media; the long forms are most common on blood-serum and potato. In tissues of animals dead from inoculation with the bacillus the length is about 2 μ, and in such cases it is usually found in pairs.

It stains quickly in aniline colors, particularly in gentian-violet,

and is decolorized by Gram's method. It has several flagella, five or less, which are easily demonstrated by Löffler's method. Spore-formation has not been observed.

BIOLOGICAL CHARACTERS. It is an actively motile, aërobic, liquefying, chromogenic bacillus. It grows in various culture media at the room-temperature; more rapidly in the incubator.

In *gelatin plates* colonies are developed in from twenty-four to forty-eight hours, and liquefaction and pigment production begin on the third day. In five days the gelatin is completely liquefied. The colonies are thin, round, and granular, with regular margins, and of a greenish color, which fades out toward the edge of the colony.

In *gelatin stick* cultures liquefaction begins in twenty-four hours, in a deep-funnel or saucer-shaped depression, constricted at the top, containing toward the bottom a white flocculent precipitate. There is a slight trace of green color in the funnel. In four days the growth has extended to the sides of the tube, then the flow of liquefaction gradually becomes level, and the liquefied portion takes a distinct green color toward the upper surface. A mycoderma forms at the top, and an abundant white flocculent precipitate collects at the bottom of the liquefied area. There is considerable change in the amount of green color from day to day; some days there is only a little at the top, and other days the green color fills the liquefied area. The green color never penetrates the unliquefied portion of the tube. In old cultures the whole tube is filled with dark-green liquefied gelatin.

On *agar-agar plates* the superficial colonies grow slowly; in seven days the largest have attained a diameter of two millimetres. The deep colonies of the same age are mere points; both are granular and regular in outline.

In *agar-agar streak cultures* an abundant, slightly viscid growth occurs along the line of inoculation in twenty-four hours. The growth is white, with a silvery sheen here and there; is slightly elevated above the surface, with thin, wavy margins; the medium throughout becomes a beautiful light green. In seven days this color becomes a very dark-green, almost black.

In *glucose agar-agar* stick cultures a white growth forms on the surface, green pigment appears near the surface, there is very little growth along the puncture, and no gas-bubbles form.

In *bouillon* a slight cloudiness appears in twenty-four hours, with a thin, white mycoderma on the surface. In five days the white mycoderma has become green, the medium quite cloudy, and a white, flocculent precipitate gradually falls to the bottom and collects there. In another five days the whole medium has become dark-green. On the surface of bouillon cultures, grown in flasks, the mycoderma is spotted here and there with silvery spots a centimetre or more in diameter. By shaking a tube or flask containing a bouillon culture the green color can be made to appear much earlier, but it soon disappears again if the tube or flask is allowed to stand. This phenomenon will be referred to later.

In the *fermentation-tube* no gas is produced in ordinary bouillon or in 1 per cent. sugar bouillon.

On *blood-serum* growth takes place actively, the colonies appearing as small circumvallate spots somewhat elevated above the surface. In eleven days isolated colonies have attained a diameter of three millimetres. The growth is quite viscid. Pigment production begins within twenty-four hours, at first a light green, but becoming dark, almost black, in five or six days. In about eleven days liquefaction of the blood-serum commences.

On *potato*, an abundant yellowish-white growth occurs in two days, later becoming brownish, and in four days the green color appears, until in about two weeks the whole potato is dark-green. The surface of the green growth is marked by many fine parallel lines resembling a thumb-print. Frequently the growth on potato shows only the brown color, none of the green pigment being present; this is evidently due to the presence of acid, for the application of an alkali brings out the green color. The "chameleon phenomenon" observed in some forms of the bacillus pyocyaneus was not seen.

In *milk*, in five days, a slight green color appears at the surface, and a white coagulum sinks to the bottom, leaving a yellowish medium above. Later the coagulum is digested, and a clear white flocculent precipitate extends up through the yellow area, while at the surface a green ring appears.

Litmus milk is decolorized.

In *Dunham's peptone solution* the growth is similar to that in bouillon. On shaking the tube the precipitate at the bottom arises in a long viscid thread, and the whole medium becomes dark-green.

All *indol* tests in this medium were negative. In *Dunham's solution* with *rosolic acid* the color was intensified, showing the production of an alkali.

RELATION TO TEMPERATURE. In all of these culture media the bacillus grows more rapidly in the temperature of the incubator (37.5° C.), and pigment production begins much earlier and proceeds more rapidly than at the room-temperature; otherwise the growth does not differ.

ALKALI PRODUCTION. The growth of the organism is attended by the production of an alkali, as is indicated by the rosolic acid solution, and the reaction of bouillon, peptone, and blood-serum cultures, to which have been added litmus, congo red, hæmatoxylin, and phenolphthalein. But perhaps the best proof of this production is the color of the green pigment itself, for this is a remarkably sensitive indicator, the green color only being present in alkaline media and quickly changing to red under the influence of acids.

PIGMENT PRODUCTION. The green pigment is produced in all culture media in which the bacillus has been grown, provided there is free access of oxygen. In gelatin or bouillon cultures, at first the color only appears at the surface, but on shaking the color appears throughout the whole liquefied area. If allowed to stand a while after shaking the color again disappears except at the surface. This phenomenon is due, perhaps, to the fact, suggested by Dr. Ernst, that the bacteria have greater affinity for the oxygen than the pigment has, and consequently the oxygen of the pigment is taken up by the activity of the bacteria, and the pigment disappears, to be formed anew when oxygen is again supplied by shaking the flask. This is partially proven by filtered cultures, in which the green color is intensified by shaking, and from which the color never disappears except when it gradually fades out under the influence of diffused light, or when it quickly disappears when exposed to direct sunlight. This phenomenon resembles somewhat the "chameleon phenomenon" of other species, and perhaps the same explanation will serve for both. Pigment is formed as abundantly at room-temperature as at the temperature of the incubator, but not so rapidly; it forms as abundantly in the dark as in the light. Cultures have been observed to lose their power of pigment production. It has often occurred that cultures from guinea-pigs killed by the germ, when made on Löffler's blood-

serum, produced no trace of pigment; but when this white growth was transferred to agar-agar tubes the pigment was abundantly produced, and when transferred back to serum tubes pigment production went on still. Cultures made directly on agar tubes from the animals produced pigment.

The presence of acid or alkali in the culture media seems to have considerable influence on the pigment production. This fact has already been referred to in the description of the growth on potato. Hydrochloric acid in the culture media to the amount of one-fourth of one per cent. inhibits the growth of the organism altogether. In a smaller per cent. of acid and in neutral media it will grow abundantly, and will produce pigment; in alkaline media it grows still better up to an alkalinity of one-half of one per cent. (NaOH), when growth ceases. In the higher per cents. of alkali, however, there is frequently growth, but no production of pigment. It seems to grow best and produce pigment most abundantly in a slightly alkaline medium. The pigment has been isolated from cultures and partially studied. If chloroform is added to the cultures the pigment is taken up by the chloroform and forms a peacock-blue, from which the solid pigment may be obtained by slow evaporation. The pure pigment crystallizes in rosettes and aigrettes of blue needles. It is soluble in water, alcohol, chloroform, and slightly in ether. It is decomposed by ammonium sulphate. Solutions lose their color and become yellow in four hours' exposure to sunlight. If any water lies above the chloroform the yellow color enters the water solution and the chloroform becomes colorless. In all its chemical reactions, so far as tested, the green pigment corresponds to the pyocyanin isolated from cultures of the bacillus pyocyaneus; but in its spectrum analysis it has been impossible to find any absorption bands, which are said to be plainly shown in sulphuric acid pyocyanin. There appears to be but one pigment produced in the cultures, while in the case of the bacillus pyocyaneus two or three are present. Further investigations are necessary to determine its character and to show whether it is identical with pyocyanin or not.

Along with the isolation of the pigment, it was noticed that a peculiar aromatic substance was taken out by the chloroform. This was found to be present in all cultures. It is remarkably persistent, and remains in all dishes which have come in contact with the chloro-

form solution for some time. An aromatic substance was isolated from cultures of the bacillus pyocyaneus by Babes.

PATHOGENESIS. The organism is pathogenic for guinea-pigs and rabbits when inoculated subcutaneously in doses of one-half a cubic centimetre or more of a bouillon culture three days old. Smaller doses (0.3 c.c.) occasion a temporary loss of weight in the animals, but no other change, except occasionally a very slight abscess at the point of inoculation.

Filtered cultures when inoculated subcutaneously in doses of one-half or one cubic centimetre do not affect the animal, except with temporary loss of weight. Animals inoculated with filtered cultures or with doses too small to prove fatal seem to be immune to further inoculations of fatal doses. Just how great this immunity is, how long it lasts, and how much of a dose is required to immunize, remain to be demonstrated.

The pathological changes in the animal organism caused by the subcutaneous inoculation of a fatal dose are an extensive inflammatory œdema about the site of the inoculation, infiltration of the subcutaneous tissue of the whole abdomen, an abundant accumulation of serous fluid in the pleural and peritoneal cavities, and, in some cases, many small points of necrosis in the liver and spleen. Smear-preparations show the bacilli in great numbers in the serous fluid of the pleural and peritoneal cavities, in the heart's blood, liver, spleen, pancreas, testes, adrenals, kidneys, and subcutaneous tissue. Cultures from all the above organs show the bacilli in pure culture. Sections of the liver, spleen, and subcutaneous tissue show the bacilli throughout the tissue in enormous numbers, apparently spreading from separate foci, which in some cases appear to surround the larger bloodvessels.

This new bacillus resembles the bacillus pyocyaneus in many respects, and perhaps is a closely related form. It differs from it, however, in the following points:

1. It is provided with several flagella scattered over its surface, while the bacillus pyocyaneus has but one, or rarely two, at one or both poles.

2. It has never been seen to grow out into chains or filaments of more than two elements, no matter in what culture medium it is grown.

3. The culture media never show fluorescence as do those on which the bacillus pyocyaneus is grown. The color is always green, with no trace of yellow, and only one pigment can be isolated; from cultures of the pyocyaneus two or three pigments can be isolated.

4. Indol is produced by the bacillus pyocyaneus, while tests of this form were negative.

5. In bouillon cultures this organism produces a cloudy medium with a thick mycoderma, unlike the corresponding changes of the pyocyaneus.

From these facts it will be seen that the organism under consideration differs from all the described varieties of the bacillus pyocyaneus, both morphologically and physiologically, and therefore must be a new species.

THE BACTERIOLOGY OF CHEESE.

(An Abstract.)

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AND

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Having been frequently called upon to examine samples of cheese believed to have poisoned one or more persons, and believing that a general bacteriological study of cheese might reveal facts of scientific interest, and possibly might be of benefit to manufacturers of this article of food, we decided to make a somewhat extended study along this line. We requested each cheesemaker in Michigan to send us not less than one pound of his product freshly cut from a whole cheese. This request has been quite generally complied with. We have also purchased samples of cheese made in other States and some from foreign countries, and have submitted all to the same examination. In this paper we shall not attempt a complete record of our work, but shall confine our remarks principally to the results obtained.

The method of examination was briefly as follows: On receipt of a piece of cheese, this was broken through the middle. The history of the cheese, when, where, and by whom made, its physical properties—its reaction determined by placing a drop of distilled water on the freshly broken surface, mixing this with the cheese by means of a sterilized platinum wire, and testing with litmus paper—were recorded. By means of a small sterilized platinum curette bits of the cheese from the interior were taken and placed in tubes of sterilized beef-tea. In the first experiments eight tubes were inoculated from each cheese. Two of these were grown aërobically at 38° C.; two aërobically at room-temperature; two anaërobically at 38° C.; and two

anaërobically at room-temperature. However, after finding repeatedly that the same germs grew in all the tubes, we omitted the anaërobic culture altogether and grew the cultures only at 38° C., in our routine work. When these beef-tea growths had continued for twenty-four hours plates were made from them, and at the same time three animals—a white rat, a guinea-pig, and a rabbit—were inoculated with the same culture. In case either of these animals died a culture was made from the blood of the heart. The surface of the exposed heart was touched with a hot iron and a sterilized tube drawn out to a point was passed through the wall of the heart and some of the blood drawn up into the tube. Plates were made from the blood thus obtained. It will be seen that by this method we employ not only the ordinary plate-method for isolating the bacteria, but in addition to this we also use the living plate, which is the animal inoculated. To any one who may criticise inoculation with mixed cultures from the cheese, we will state that every toxicogenic germ found by us was tested in pure as well as in mixed culture. To any one who may object to intraperitoneal inoculation, we can say that all the toxicogenic bacteria were tested on the above-mentioned animals subcutaneously and intravenously as well as intra-abdominally. They were also tested on white mice in addition to the three animals employed as living plates.

We cannot claim that we have obtained pure cultures of every kind of bacterium in the sixty-five different makes of cheese examined by us, but we did find some that are of more or less interest. We endeavored to find not only the bad bacteria, but we looked for some of the good ones as well. We were quite as much interested in ascertaining whether or not there are peptonizing bacteria in cheese that do not elaborate any poisonous products as we were in finding toxicogenic germs.

Of the sixty-five samples of cheese examined in the above-described manner six had been suspected of having poisoned one or more persons. Of these poisonous samples three were of Michigan manufacture, and one each from New York, Illinois, and Wisconsin. Of the sixty-five kinds, forty-nine were the ordinary American cheese. Each of these contained a toxicogenic bacterium. Of the others, one imitation Edam, said to have been made in New York, two imitation Swiss, one Roquefort, one genuine Swiss, one Stilton, one Dutch, one

genuine French, and one sap-sago contained no germs which in any amount had any appreciable effect on the animals employed. Three imitation Neufchatels, two imitation Limburgers, and one English dairy, said to be imported, contained the same toxicogenic germ found in the ordinary American cheese.

In this abstract we shall confine our remarks to the two classes of germs which we regard as of most importance. The poisonous germs found in the forty-nine samples of cheese belong to the same group, although minor differences were easily detected among them. From each of these cheeses this germ was obtained in four cultures, both by the ordinary and the living plates, and the morphology and toxicology of each were studied. There were found to be some differences in virulence as well as in forms of growth. The gelatin colonies were generally yellowish spheres, but many appeared in the form of rosettes. All gave the indol reaction. However, many germs that do not belong to this class gave the same reaction. Therefore this test cannot be used to distinguish a good from a bad cheese. Of the sixty-five samples examined, only four contained no germ that gave the indol reaction. These were the Roquefort, the genuine Swiss, the genuine French, and the sap-sago. All the poisonous germs coagulated within seventy-two hours; but three, from different samples, differed greatly in the promptness with which they caused coagulation. There was no cheese that did not contain a coagulating bacterium. None of the poisonous bacilli liquefied gelatin. All grew abundantly on agar surface, but the general appearances of these growths showed considerable variation. The same is true of their growth on potato. In motility the poisonous bacilli showed quite a range of variation. Generally they were non-motile, but some were quite active. It is quite evident that all the poisonous germs found in these cheeses belong to the colon-group.

Several attempts were made to increase the virulence of this germ by making cultures from both the peritoneal fluid and the blood of the heart. While these attempts were partially successful, we did not succeed in obtaining a culture of very high virulence. Of the most virulent growth obtained, ¼ c.c. of a beef-tea culture twenty-four hours old was the smallest amount fatal to full-grown rabbits when injected intra-abdominally. The heightened virulence was shown more markedly by the shorter time necessary to cause death than by absolute

decrease in the minimum fatal dose. The time was reduced from twelve to two hours. With the most virulent cultures the post-mortem appearances after intra-abdominal inoculation were as follows: On cutting through the abdominal wall the loops of small intestines appear as a gelatinous mass. The peritoneal coat of the cavity is congested, and numerous pin-point hemorrhages may be seen in it. Large blood extravasations may be found in the mesentery where it leaves the intestines. The contents of the intestines are yellowish fluid and contain gas. The omentum often shows numerous hemorrhagic spots, which are most marked along the free border. The amount of fluid in the peritoneal cavity varies with the rapidity with which death results, and is not proportional to the quantity of fluid injected. In one instance in which the amount of culture injected was only ¼ c.c., death did not occur until thirty-six hours after inoculation, and there was drawn from the peritoneal cavity 9 c.c. of bloody fluid. This animal had hemorrhages from the nose and mouth before death. However, individual differences in the quantity of fluid found in the peritoneal cavity were not always in accord with the above statement. It was a noticeable fact that while the heart in guinea-pigs and rabbits, after death from this germ, was quite uniformly in diastole, this organ in rats was quite as constantly in systole, and empty.

A flask of beef-tea was inoculated with this bacillus and kept in the incubator. From time to time, as the following results will show, rabbits of practically the same weight were inoculated with this culture:

January 27, 1897. Rabbit received 2 c.c. of this culture, now one day old. Remained well.

28*th*. Rabbit received 2 c.c. of this culture, now three days old. Remained well.

29*th*. Rabbit received 2 c.c. of this culture, now three days old. Died within twelve hours.

31*st*. Rabbit received 2 c.c. of this culture, now five days old. Died within twelve hours.

February 1*st*. Rabbit received 2 c.c. of this culture, now six days old. Lived.

2*d*. Rabbit received 2 c.c. of this culture, now seven days old. Lived.

3*d*. Rabbit received 3 c.c. of this culture, now eight days old. Lived.

These experiments show that beef-tea cultures of this bacillus first increase in virulence and then decrease. As much as 10 c.c. of cul-

tures fifteen days old, or older, were injected into rabbits intra-abdominally without effect.

The following experiments show that the simultaneous injection of morphine and inoculation with the bacillus intensify the effect of the latter. We were led to make these experiments because one of us had been convinced, from observation of cases of food-poisoning, that the administration of morphine is dangerous. We fancy that the administration of morphine in appendicitis is often unwise for a like reason. However this may be, we herewith reproduce our record:

Pig No. 77 had ¼ grain morph. sulph. hypodermically. No effect.

Pig No. 78 had ½ c.c. of culture of this germ. No effect.

Pig No. 79 had ½ c.c. of the culture, and immediately afterward ¼ grain of morphine. Death within twelve hours.

Pig No. 80 had ¼ c.c. of the culture. No effect.

Pig. No. 81 had ¼ c.c. of the culture, and immediately afterward ¼ grain of morph. sulph. Found dead twelve hours later.

These experiments were repeated, with like results in all instances. The reader can make such application of these facts as he may deem wise.

A quantity of this germ in a dried state was obtained by washing the growths from a large number of Roux flasks with distilled water, collecting the germ after twenty-four hours in a centrifuges and drying at 40° C. in vacuo. Steaming, boiling, and the action of absolute alcohol do not destroy the poison. The toxin of this bacillus is a constituent of the cell, and when the cell breaks down in old cultures the toxin is destroyed. It will be seen from this that whether a cheese containing this germ be poisonous or not, probably depends upon the amount of germ in the portion entire and the susceptibility of the individual. We are not prepared to state whether this bacillus actually multiplies in the animal body or not. The dead germ kills as quickly as the living. Whether the former must be employed in larger amount in order to accomplish the same result or not, we cannot say.

We will only mention the other class of germs which we have found in cheese and which we regard as important. These are peptonizing bacilli. Some of these digest casein quite rapidly at the temperature of the body, and neither they nor their products have any visible effect on the animals employed by us. Some of these develop in milk a rich yellow color and a nutty flavor.

These two classes of germs are easily separated by means of heat. A temperature of 65° C. (144° F.), maintained for three minutes, kills the poisonous germ, while the same temperature continued for thirty minutes is without effect upon these peptonizing bacilli. Milk can be Pasteurized at 70° C. (158° F.) without appreciably affecting its taste. This might be done with milk used in the manufacture of cheese, and either before or after Pasteurization a selected peptonizing bacillus might be added to the milk. However, whether this suggestion prove of practical value or not practical trial alone can demonstrate.

The poisonous germ described in this paper must not be confounded with that described by Perkins and one of us two years ago, nor does it produce the powerful poison obtained by one of us in 1884, and known as tyrotoxicon. Every bacteriologist knows that the harmful germs that may find their way into milk are numerous, and only the ignorant will be disappointed when they fail to find the same toxin in all samples of poisonous cheese.

DISCUSSION.

DR. H. C. ERNST: In Dr. Vaughan's experiments with the quarter-grain doses of morphine, I would like to ask whether he attempted to run down the dose a little more in proportion to the size of the animal, as demonstrating the possibility of its being the toxic effect of the drug which was fatal. Would it not be a good plan to carry out such experiments? One-quarter grain of morphine seems to be a large dose for so small an animal.

DR. S. J. MELTZER: Morphine retards the absorption, not only from the intestines, but also from the peritoneal cavity, and probably also from the subcutaneous tissue. The fatal effect of the morphine might be explained by the retarded absorption, and therefore also retarded excretion, of the toxins from the body. Another point might be suggested, that by the hypodermic injection some injury is done to the tissue, and thereby, according to our experiments, a new focus is prepared for the settlement of the bacteria. Netter and others explained in this way the abscesses produced by hypodermic injections of ether, etc., in cases of pneumonia. I would like to know whether Dr. Vaughan has tried the effects of injections with some other substances.

DR. VAUGHAN: Guinea-pigs bear morphine very well indeed. The experiments were made in groups like this: one guinea-pig had an injection of a quarter grain of morphine, a second received one-quarter c.c. of the culture, and a third was given both. The first two were not affected, but the third died. I did not try smaller doses.

A CASE OF TWO ISOLATED CARCINOMATOUS GASTRIC ULCERS:

Apparent Recovery after Exploratory Cœliotomy; Death eighteen months later, following a Second Operation; Hyperchlorhydria to the End.

By D. D. STEWART, M.D.,
of Philadelphia.

It is accepted that in approximately 5 to 8 per cent. of all cases of cancer of the stomach the growth has had origin about the cicatrix of a previously existing simple ulcer or in the margin of one still open.[1] Cases, however, of complete transformation of an open ulcer into carcinoma, forming the *ulcus carcinomatosum*, are much more rare,[2] and are of no little interest and importance, representing, as they do, a group, the diagnosis of individual cases of which is often most difficult.

It is not to the review of the literature of these that attention is now directed, but to the consideration of a recently encountered case about which several curious features are centred, that cause it to stand somewhat apart and render it worthy of isolated report.

The points of special interest are that eighteen months before the patient came under the writer's observation the ailment was regarded as one of carcinoma of the stomach by the surgeon, Dr. Keen, who at that time did an exploratory cœliotomy. The body of the stomach was then apparently so much involved in the presumed cancerous process that the idea of a gastro-enterostomy, previously entertained, was

[1] The carcinomatous degeneration of the margin of the cicatrix of an ulcer, I believe, was first pointed out by Brinton. Rosenheim considers that from 5 to 8 per cent. of gastric ulcers become carcinomatous. Zeitschrift f. klin. Med., Bd. xvii., and Berl. klin. Woch., 1889, p. 47.

[2] According to Hemmeter (Medical Record, September 11, 1897), who has recently reviewed this subject, about twenty-eight are on record.

abandoned. What appeared to be two small glands in the omentum were removed, and one was found to be a metastatic cancerous nodule. A seeming return to perfect health followed the section, with a gain in weight at least ten pounds in excess of that ever weighed before. Dr. Keen reported the case nine months later as to all appearances completely cured. The symptoms subsequently recurred. Through the kindness of Dr. Keen, the case, then, after a lapse of eighteen months, came under the writer's observation. The indications were now rather of chronic ulcer, and but for the knowledge of the removed cancerous nodule it would in all probability have been so diagnosed. No tumor existed; the stomach was normally placed and undilated; the secretory function was normal; motility was lowered; the patient could eat and digest a hearty meal without pain or discomfort. A digestive leucocytosis was present, and a pathological leucocytosis, as concerns absolute increase in number of leucocytes, absent. The skin was of cachectic hue, but the patient had lost only a minor part of the large amount of weight gained after operation, and his physical condition was relatively remarkably good. A second exploratory cœliotomy disclosed what appeared to be an entirely healthy stomach save at one point, at which was discovered a very large ulcer. The patient died as a result of septic peritonitis. The necropsy showed two very large distinctly isolated and widely separated carcinomatous ulcers, while the remainder of the stomach except the pylorus, which was the seat of simple fibrous thickening, was perfectly healthy.

The patient, J. H. K., was a physician, aged fifty-two years. He had never had syphilis. The family history was fair; parents and grandparents had all died of old age, with the single exception of his mother, who had succumbed to presumed gastric cancer when aged sixty-five years. When in his best condition his body-weight held between 155 and 165. This last weight had, previous to the first operation, never been exceeded. He had had typhoid fever when aged twenty-two years. Diarrhœa of about a year's duration succeeded. Otherwise he had been free from illness until within the past six years; although for nearly twenty years, as was elicited on careful inquiry, he had had more or less neurotic disturbance of digestion, apparently of the nature of hyperchlorhydria, occurring chiefly when he was overworked or subjected to excessive mental strain. He was of a nervous disposition and of easily disturbed mental equipoise. A hard-working country practitioner, his habits of living were irregular as concerns eating and sleeping. In December, 1890, his mother, to whom he was much attached, died. She had had symptoms of gastric cancer, the duration of which ailment was about a year.

Her illness and subsequent death worried him a great deal. He lost appetite and fell off in weight and strength, and was much constipated. His ailment was regarded as a mere nervous indisposition, for which a change of air was suggested. After a few months spent in California he gained in strength and weight, and remained in fair condition for over a year. But anorexia, constipation, and a tendency to heartburn and pyrosis continued. Actual pain was apparently never present. There was, however, a sensation of distress and uneasiness, which appeared several hours after a meal, associated with heartburn. These sensations were felt in the epigastrium, and often extended posteriorly to a point immediately below the inferior angle of the right scapula. This is as he described his symptoms to me. In Dr. Keen's notes, taken just before the first operation, it is stated that he suffered from much gastric distress six years ago, and "a sense of weight and pressure extending through the body from the pit of the stomach to the back to a point to the right of the spine on a level with the lower angle of the scapula." He finally abandoned practice almost entirely, devoting himself to travel. His health was now, on the whole, fair until the latter part of February, 1896, two-and-a-half months before he came under Dr. Keen's observation. Then he had an attack of influenza. A sudden and profuse gastric hemorrhage occurred early in March, 1896. About a quart of blood was said to have been vomited, and a pint afterward escaped by the bowel. No aggravation of the gastric symptoms had preceded the hemorrhage, and the severe hemorrhage did not recur. But subsequently to the time of operation (five weeks) he vomited very frequently a dark-looking fluid, recognized by his attendant, Dr. Wright, of Erie, as altered blood. During the greater part of this time he was nourished almost solely by the bowel. From his former weight of 160 pounds he had fallen, during the six years, to about 130 pounds. As a result of the hemorrhage and the five weeks exclusive bowel-feeding, there was a further loss of about fifteen pounds. He was first seen by Dr. Keen, May 13, 1896. A history of the case, very much as is stated, was elicited by Dr. Keen, who also noted that his color was decidedly sallow, and that "he appeared as one who had lost much strength and was quite sick." A physical examination by Dr. Keen[1] disclosed no disease in the organs of the chest or in the kidney. No abdominal tumor could be made out, but "a distinct sense of marked resistance was apparent in the epigastrium." The debilitated condition of the patient rendered it unwise, in Dr. Keen's opinion, to make a study of the condition of the stomach by the employment of the tube. Nothing is therefore known of the condition of the secretory function at this time. An exploratory cœliotomy was now determined on by Dr. Keen, "the expectation being that a cancer of the stomach would be revealed." To quote from Dr. Keen's report, just referred to:

"The operation was done May 22, 1896. There were present during the operation, Professor J. H. Etheridge, of Chicago, Dr. W. A. Edwards, of San

[1] See Dr. Keen's paper, "Tuberculosis or Carcinoma of the Stomach: Exploratory Cœliotomy, Subsequent Apparently Complete Cure." Annals of Surgery, June, 1897.

Diego, Cal., Dr. J. J. Buchanan, of Pittsburg, and Drs. J. M. Baldy, William J. Taylor, and George W. Spencer, of Philadelphia. A vertical incision was made through the middle of the left rectus. The stomach immediately presented and was drawn out. The site of the disease was found to extend toward the cardiac extremity of the stomach, and, in order to reach it fully, the incision was extended upward to the border of the ribs. Even then it was only possible to bring about half of the stomach into the abdominal opening and almost none of the upper end. By holding up the abdominal walls, however, a view of nearly all the stomach was obtained. From the cardiac end toward the pylorus the disease extended as an infiltrating growth, both anteriorly and posteriorly, over an area extending over nearly the whole of the stomach. It did not reach quite to the pylorus. The mass was nodulated, hard, and thick, and every one present believed that it was cancerous. It was so extensive that no room was left for a gastro-enterostomy, so the abdomen was closed. Before doing so two enlarged glands in the great omentum were noted, and around one of these a ligature was cast, after which it was removed for microscopic examination.

"The patient made an uninterrupted recovery. Shortly after the operation he began to take liquid, and then semi-solid food, and soon afterward solid food, and left the hospital about three weeks after the operation, having not only recovered from the operation, but being, apparently, on the high road to health. Dr. Keen was much surprised when, later, Dr. Kyle made the following report: 'Certain areas showed small nodules surrounded by dense fibrous tissue. The bloodvessels, while not entirely obliterated, showed thickening of the walls, especially the intima. It is undoubtedly tubercular.'

"In August, three months after the operation, he reported that his weight had increased to 171 pounds, and in October it had risen to 178½ pounds; his appetite, digestion, and assimilation were excellent, and he suffered no pain. In fact, his only trouble was an occasional sleepless night. His diet in August consisted of 'bread and butter, milk, eggs, potatoes, beefsteak, mutton, fish, rice, oatmeal, and fruit.' He had been taking some syrup of the hypophosphites and cod-liver oil in consequence of Dr. Kyle's report.

"Dr. Keen said that he had mentioned the names of the gentlemen present for the especial reason that those present at the operation, all men of large experience, agreed that the disease was unquestionably carcinoma of the stomach."

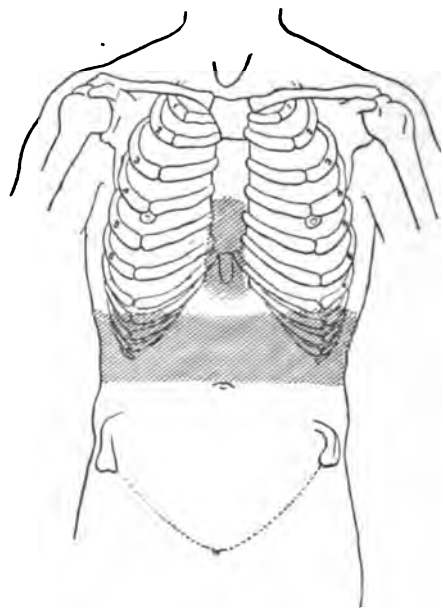
The apparent recovery of the patient had caused Dr. Keen, at first, to accept the view of Dr. Kyle, who first examined the removed nodule and gland, that the condition was one of tuberculosis. Later, but immediately subsequent to the publication of Dr. Keen's report, and long before the patient again came under observation, sections from the supposed tubercular glands were submitted to Dr. Welch, of the John Hopkins School, to Dr. Councilman, of Harvard, to Dr. Adami, of McGill University, and to Dr. Prudden, of New York.

These all reported no evidence whatever of tubercle, but that sections from the nodule showed it to be undoubtedly a metastatic cancer. Dr. Welch regarded it as scirrhous; Dr. Councilman, as an adenocarcinoma; Drs. Adami and Prudden spoke of it as simply cancer. The preparations of the sections sent were regarded to be so poor that the exact character of cancer was somewhat in doubt. Dr. Councilman, however, pronounced it positively to be an adenocarcinoma.

The subsequent history of the case is as follows:

The patient was referred to the writer by Dr. Keen in December, 1897, seventeen months following the operation. On getting about after the operation he had improved wonderfully in health, all gastric symptoms for a time practically disappearing. He gained rapidly in strength and flesh, so that at

FIG. 1.

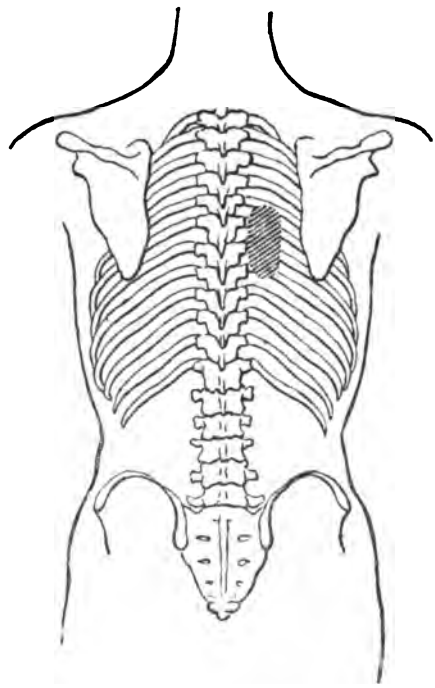


The two areas shaded are those of pain, as described.

the end of five months he weighed nearly fifteen pounds more than he ever had before (175). During this time he had not resumed practice, but took every care of his health. After he had held this maximum gain about five months he began to lose weight without assignable cause. He had no gastric symptoms during this time; no epigastric distress, sour stomach, or nausea. He

had, as was common with him for a number of years, but little appetite, and slept badly, and he was considerably disturbed by cramps in the calf muscles. He now spent several months in the mountains, and in September, 1897 (sixteen months after the operation), he returned to his home feeling in very good health and weighing 166 pounds. Shortly after this (October, 1897) gastric symptoms reappeared. These were nausea and occasionally a tendency to vomit if he ate very heartily. Heartburn or pyrosis was never evident. A regurgitation, which he described as "cold sweet water," occurred once

FIG. 2.



The shaded area is the dorsal site of pain, as described.

or twice weekly. Because of loss of appetite he has lately been living largely on milk punches. About the middle of October, 1897, he began to feel gastric pain, and with its appearance a rapid drop in weight occurred (twenty-six pounds in two months). The pain was in the region of the sternum, the dorsum, and the epigastrium. The sternal pain occupied a space from mid-sternum to a distance midway between the tip of the ensiform appendix and the umbilicus, and about three inches in breadth. (Fig. 1.) This pain he described as most prostrating. He regarded it as intimately related, in characteristics, to a dorsal pain of most annoying character, the situation of which was, invariably, immediately to the right of the spinal column, between

it and the vertebral border of the scapula, and extending from the fifth to the eighth ribs. There was also a diffuse pain in the epigastrium and both hypochondria. These pains were all invariably more severe at night after retiring, especially that in the dorsal region. Otherwise the character of pain was interesting in that it was commonly felt, as in the pain of hyperchlorhydria, at a time after food when an excess of free hydrochloric acid becomes marked. Taking food, and especially meat, almost invariably relieved or removed all pain. Drinking freely of water, such as Vichy, also relieved the pain, although not to the extent that food did. The use of sodium bicarbonate, however, had no marked effect.

Unprovoked vomiting was unusual, and had not occurred for some time. He had formed a habit some weeks before I saw him of each morning drinking a pint or so of warm water containing sodium bicarbonate, and then emptying the stomach by regurgitating its contents. He could in this way relieve himself of any discomfort experienced. The rejected material rarely contained food eaten the night before. He stated there was usually a good deal of mucus, and that occasionally evidences of blood were noted. Inspection of the regurgitated matter showed it to contain altered blood. It was quite coffee-ground in character. He had been subject to constipation for years. The patient's skin was of cachectic hue. His general condition was really very good. His weight was 149 pounds, within ten to fifteen pounds of his best weight when in good health, and nearly thirty pounds in excess of his weight eighteen months before. During the two weeks he was under observation it was interesting that he gained seven pounds, indicating the still well-preserved recuperative power.

Physical examination of the organs of the chest revealed no abnormality; the lung showed no sign of disease, and the heart was fairly strong and free from murmurs.

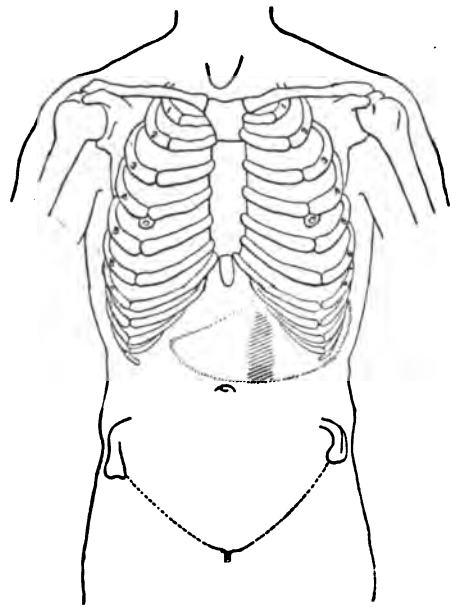
The abdominal wall displayed the healed cicatrix of the preceding cœliotomy. Indications of local or general resistance in the stomach region, or of tumor, and abnormal glandular enlargement anywhere, were absent. The liver and spleen were normal in outline. The inferior portions of both kidneys were palpable only on full inspiration. The stomach, by ordinary percussion, by auscultatory percussion, by gaseous inflation, and by transillumination, was found to be normally placed. Indeed, by gastro-diaphany, as is here illustrated, it was found to occupy a position considerably higher (three-fourths of an inch above the umbilicus) than is usual when the normal stomach is fully distended with water, as the organ was at the time of this illumination. The cause of this was subsequently made apparent (adhesions to the abdominal wall and to liver). The transillumination with a lamp of three candle-power was perfect, the anterior surface of the organ being beautifully mapped on the abdominal wall. The scar area alone was shaded somewhat.

Examination of the urine showed it to be free from albumin, glucose, and casts.

For some time, as was previously stated, thinking that washing out the

stomach would be beneficial, and disliking to employ the tube, his habit was to drink water and regurgitate it. He was able to report that food, other than in traces, was never present in the morning.

FIG. 3.



Transilluminated area, with shaded area of scar; stomach containing 1100 c.c. water.

The examination of the stomach contents was as follows:

December 7, 1897. Stomach washed and 500 c.c. of rather thick oatmeal gruel, flavored with salt, administered. Two and one-quarter hours subsequently, 300 c.c. were removed, practically all that remained, as was shown by subsequent lavage. Removed contents were dark red, showing on standing a copious dark sediment. The filtrate was clear. T. A. = 72; HCl = 0.2 per cent.; acid salts = 13; no lactic acid. Starch converted into erythrodextrose. Test for lab-zymogen: 10 c.c. milk, at 40° C.; 2 c.c. filtrate; solidification of the milk occurred within two minutes.

8th. Stomach washed and 500 c.c. thick oatmeal gruel administered; 320 c.c. remaining in two and one-half hours; coffee-ground sediment as before. Upper stratum on standing, reddish hue. Filtrate not bloodstained. T. A. = 66; HCl = 0.1916 per cent.; acid salts = 15. No organic acids. Eyrthrodextrose as before. Lab test under same couditions as above, positive in the same time.

Digestion test: in incubator at 40° C., egg disk approximately $\frac{1}{2}$ c.m. square, by $\frac{1}{10}$ c.m. thickness; in each, 10 c.c. filtrate. One phial reinforced by an

active preparation of pepsin. The disk in the phial unreinforced by pepsin had entirely disappeared in three hours; there were still faint remains of the disk in the phial in which pepsin had been added. The disks were of the same size, but, as they were not accurately weighed, that in the pepsin solution might have been a trifle larger, and, hence, caused this difference. This test was repeated with the filtrate from two other trial meals, and showed that the addition of pepsin produced no earlier disappearance of the egg-disk than if it had not been added. It showed that secretion of pepsin was in the same vigorous proportion as the HCl.

It should be here remarked that the gruel meal on each occasion caused considerable gastric distress and pain, all of which disappeared instantly on their removal and washing out the stomach.

9th. After lavage, a large, thick, tenderloin steak, 60 grammes of bread, 360 c.c. of milk were eaten. Four hours later 300 c.c. quite fluid contents were removed by aspiration. A fair amount remained, as was shown by a subsequent lavage: Contents not bloodstained, although much retching was produced by the use of the tube. T. A. of filtrate = 151; HCl = 66. The digestion test was as above stated.

13th. The same meal taken as on December 9th. Removed at the same interval 300 c.c. No blood; contents of natural appearance. T. A. = 144; free HCl = 72.

It is noteworthy that, as remarked, while with the gruel meal gastric distress was always felt, relieved only by the removal of the meal and subsequent washing, not the slightest trace of pain or discomfort was experienced during the digestion of the full meal of steak, bread, and milk. During the two weeks he was under observation this was found to be invariable in many trials. He could eat and digest with relish and freedom of symptoms a steak of good size.

Blood examination, December 9th. Red blood-corpuscles, 3,528,000. Hg. 46. This examination repeated later gave practically similar results. In the morning, fasting, leucocytes, 5940. Three and a quarter hours after a large tenderloin steak, milk, and bread, the leucocytes count was 7700; three-quarters of an hour later the count repeated was 8000.

Second day's examination. Nothing save oatmeal gruel had been taken, leucocytes, 6500. Four hours after a large tenderloin steak, bread, and milk, the count was 9000. These examinations were very painstakingly carried out, and may be regarded as entirely accurate. They show absence of pathological increase in the number of leucocytes, and the presence of a normal digestive leucocytosis. A differential count (1350 leucocytes) gave interesting results:

Polymorphonuclear neutrophiles	79.00	per cent.
Small lymphocytes	13.63	"
Large lymphocytes	3.46	"
Transitional lymphocytes	2.42	"
Eosinophiles	1.49	"

This showed the presence of a pathological leucocytosis, despite the absence of an increase in the total count, which on this occasion was 6500.

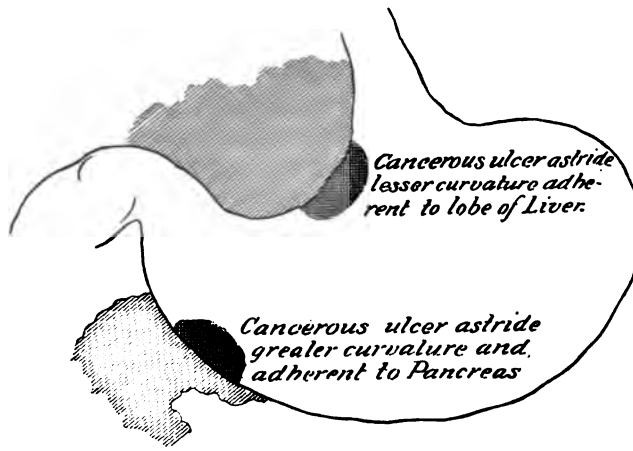
After this outlined study of the case, the opinion was given that the original trouble had been a long-existing hyperchlorhydria; that this, in all probability, had some years back been succeeded by ulcer, and that the ulcer had at least two years before undergone carcinomatous degeneration. Of course, this last statement would have been impossible but for the knowledge of the removal of the metastatic nodule. Indeed, but for this, the diagnosis of cancer itself at this time, in view of the history of the case since the operation, would have been seriously in question. The growth was regarded as being in the body of the stomach, not encroaching on the pylorus. The diminished motility was presumed to be due to weakness of the musculature, through carcinomatous infiltration of the stomach wall. To this opinion I had Dr. Keen's concurrence. The patient placing himself in our hands, a second exploratory cœliotomy was advised, as at least offering a chance of again temporarily arresting the progress of the cancer. It was, moreover, hoped that an opportunity might be afforded for an excision of the growth, or, indeed, of a part or the whole of the stomach, should indications of external metastasis not be present.

Second operation by Prof. Keen, December 23, 1897. The anterior wall of the stomach was found to be extensively adherent to the abdominal parietes over a large area. On incision of stomach, its interior, as far as could be seen at first, presented a healthy appearance. Its wall was thinner than normal, but the mucous membrane everywhere looked normal. Palpation revealed no thickening anywhere except posteriorly and superiorly near the œsophagus, at which point a circular hard ridge of some size could be felt, and afterward was seen. This mass appeared to be a very large ulcer, with elevated callous edges. A small clipping from the edge was removed for microscopic examination. The ulcer was too close to the diaphragm and too far from the incision to permit of its removal, or of the removal of the stomach itself, because of the extensive adhesions. It was concluded to establish a duodenal fistule to permit of feeding in this way, so that, as is remarked by Dr. Keen in his notes, "If the ulcer be a non-malignant one it would heal within two or three weeks; if malignant, the rest to the stomach would, at least, do no harm." The patient, unfortunately, after the first few days did badly. Obstinate hiccough appeared; the external wound failed to heal, and he succumbed finally, eighteen days after operation, to a septic peritonitis.

The necropsy was performed by Dr. Keen eighteen hours after death. Through a misunderstanding, the body had not been placed on ice, and was already somewhat advanced in decomposition. The whole external wound

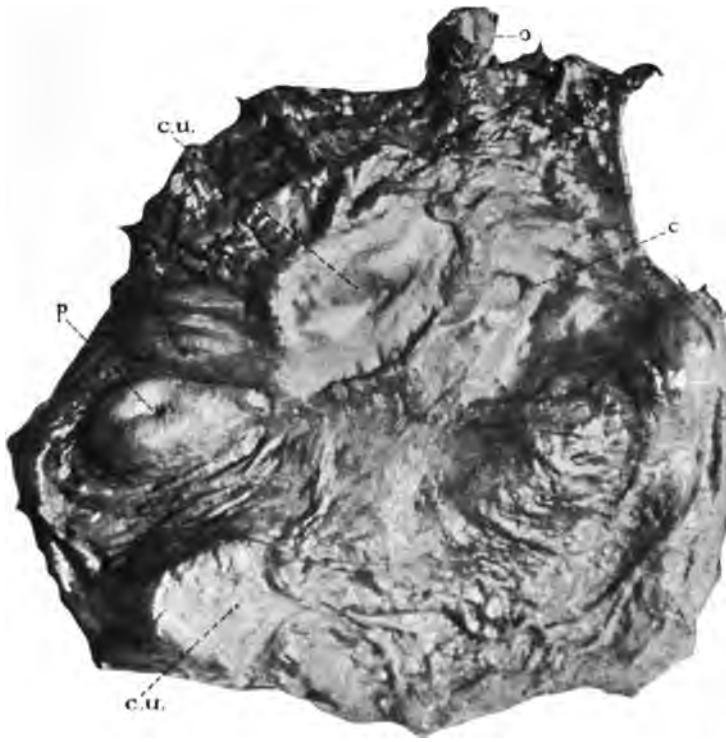
gaped, with protrusion of stomach and intestine. The peritoneal cavity contained considerable pus. The heart and lungs were healthy. The liver was somewhat enlarged and pale; no evidence of metastasis here or in the peritoneum could be found. Spleen and kidneys appeared healthy. The stomach was normally placed and undilated. It was adherent to the abdominal wall, and superiorly, through the entire length of the lesser curvature, to the under surface of the left lobe of the liver, and posteriorly, at the base of the lower ulcer, to the pancreas. The pancreas appeared normal, and microscopic examination subsequently disclosed that it was so. Section of the stomach showed some softening of its walls due to post-mortem changes. Two large and entirely isolated ulcers were now noted. One, the nearest edge of which was 1¼ cm. from the cardiac orifice, was astride the lesser curvature, with the larger portion toward the posterior wall. It was adherent by its base to the inferior surface of the left lobe of the liver. This ulcer was in the largest diameter 8½ cm., and transversely 6 cm. It was of ovoid shape, with crater-like, raised, thickened edges. The margins were especially prominent on the

FIG. 4.



portion nearest the cardia; here the edge measured in one part 1⅛ cm. The floor of the ulcer was indurated, smooth, and depressed, and adherent to the left lobe of the liver. The second ulcer was situated astride the greater curvature, 7 cm. from the pylorus. It was of circular outline, with thickened, elevated, sloping edges, like the first described, and with a slightly excavated, considerably indurated centre. This ulcer was adherent to the adjacent part of the pancreas. It measured 5 cm. in length by 4½ cm. in breadth. The edges of both ulcers were œdematous, hemorrhagic, and somewhat polypoid. Immediately surrounding the ulcers the stomach-wall was somewhat indurated, but this was not evident for any distance. There was apparently no connection between the two ulcers, which were widely separated, as is shown in the accompanying cut and in the photograph.

FIG. 5.



C. Cardia.
C. u. Carcinomatous ulcer.
O. Œsophagus.
P. Pylorus bulged into the stomach in order to show the thickening and narrowing.

The lumen of the pylorus was narrowed through fibrous and muscular thickening of its wall. It admitted with difficulty only the tip of the index-finger.

The specimen was first given to Dr. A. O. J. Kelly, to remove portions for microscopic examinations. Subsequently portions of the growths were sent by Dr. Keen to Drs. Welch, Councilman, Adami, and Prudden.

Dr. Kelly's report is as follows:

Microscopical Examination. The specimen had been placed in alcohol, but is in a very poor condition. Some areas are in a state of putrefaction and do not permit of a careful study of histologic details. This is especially true of the larger ulcerated area situate on the posterior wall toward the lesser curvature. The smaller ulcerated area situate at the posterior-inferior region toward the greater curvature is in a fairly good state of preservation.

Sections through the edge of this latter ulcerated area reveal a carcinomatous new growth arising from the mucous coat, implicating the latter, and also the submucous, the muscular, and the subserous layers of the wall of the organ. The mucous and submucous coats are entirely replaced by the new growth; the muscular and the subserous are also considerably invaded and to a less extent replaced. The growth consists of cells arranged in alveoli and surrounded by a connective-tissue stroma. The alveoli, which pervade the tissues in all directions, vary greatly in size and shape. For the most part they are elongated and narrow. Others are much wider and very irregular. The cells are of distinctly epithelial type. They commonly line the alveoli, leaving a central lumen, which is in some places free, in others more or less filled with detritus. Other alveoli, in addition to being lined by the cells, are completely filled by them. The cells are predominatingly high-cylindrical in shape, especially those which line the alveoli and leave a clear lumen. Other cells constituting the periphery of solid nests of cells appear more cubical. Still others, and all situate toward the centre of the alveoli, are polymorphous. The cells reveal distinct nuclei, which stain readily; those of the cylindrical cells being situate toward the base of the cells. Nucleoli are also discernible. There are at present a few karyokinetic figures which are generally hyperchromatic. Many of the cells, especially those situated toward the centre of the nests, reveal various retrograde metamorphoses. The stroma, which consists of fully developed fibrillar connective tissue, varies considerably in different regions. In places it is abundant, in others scanty. Its nuclei present some karyokinetic figures, and the tissue itself is the seat of considerable round-cell infiltration, which latter exhibits many evidences of retrograde changes. The bloodvessels, particularly the larger ones, manifest, for the most part, thickened walls. Toward its free surface the neoplasm is markedly necrotic, and this process is complete at the central area of ulceration, where it extends to and implicates the muscular coat of the stomach. The latter is markedly hyperplastic. This, together with the fibrous overgrowth, mainly of the submucous coat, and the tumor-mass

itself, occasion the marked thickening and polypoid condition of the edge of the ulcerated area. Away from the seat of ulceration there is a gradual transition from the tumor-alveoli to apparently normal gastric tubules. There first occurs a diminution of the obviously neoplastic alveoli, then a succession of irregular gastric tubules, and finally apparently normal tubules. Nests of cancer-cells also invade the muscular coat for a short distance from the ulcerated edge. These transitional stages, however, apparently do not implicate more than 1 to 1.5 cm. of the stomach-wall beyond the ulcerated edge. A section 2 cm. from this edge fails to disclose any noteworthy deviation from the normal.

Sections through the edge of the larger ulcerated area, situate toward the lesser curvature, reveal conditions which, as far as can be definitely determined in view of the decomposed state of the specimen at this region, are entirely analogous to those already detailed in connection with the smaller ulcerated area. The alveoli, however, are in many instances much larger, and the cells arranged much more irregularly. In the deeper layers of the stomach-wall there are a few cystic spaces lined with cylindrical epithelium.

Sections through the pylorus reveal it to be 1 to 1.2 cm. in thickness. Both the muscular and the fibrous layers of the wall are implicated in this overgrowth. There is no carcinomatous invasion of this region. Sections from two areas between the two ulcerated surfaces fail to reveal any evidences of carcinomatous alteration. The structures here present no especial deviations from the normal. The same is also true of sections from a region near the pylorus between the ulcerated areas.

DIAGNOSIS. Double ulcerated adenocarcinomas of the stomach. Each ulcerated area singly considered presents no especial deviations from that type of carcinoma of the stomach of which these are instances. The interest in the specimen centres in the fact that in the same stomach there are found two carcinomas apparently unconnected with each other. There is no diffuse carcinomatous infiltration of the wall of the stomach, and aside from the marked thickening of the pylorus and about the ulcerated areas, there is no especial implication of the fibrous connective tissues, certainly no diffuse pathological alteration of this structure.

The others, except Dr. Prudden, reported similarly, that sections from the portions of the two ulcers submitted showed them to be ulcerated typical adenocarcinomas. Dr. Prudden briefly reported that the growths were carcinomatous. The specimen had not been well preserved when the portions were subsequently sent to the others. Dr. Welch, in his report to Dr. Keen, after remarking on the badly preserved condition of the specimens sent him, which made study of them somewhat difficult, said that the essential points could be determined. There could be no question as to cancer and its type, and

that a careful search revealed no distinct evidences of disease for a distance of much more than 1 cm. beyond the ulcers.

There are several features in this case of very special interest. The early history left little doubt concerning the existence of a long-standing gastric neurosis with associated hyperchlorhydria. That one or more gastric ulcers should appear in a subject of chronic hyperchlorhydria, debilitated by grief, overwork, and inanition—induced both by these causes and by total anorexia superadded to long-existing indigestion—cannot be a matter of surprise. Nor could it that a simple peptic ulcer should subsequently be the seat of carcinomatous transformation. Such cases, though not numerous, are on record. The features which, however, are most interesting about the case are as follows: The apparent extensive disease of the body of the stomach at the time of the first operation; the apparent recovery of the patient and the surprising increase in weight to a point beyond that ever reached in health, and its maintenance for so long a time in one then the probable subject of two separate carcinomas, which had already given rise to a nodular metastasis in the omentum; eighteen months subsequently the fairly good physical condition; the really small loss from the weight usual in health—this was in a measure explained by the remarkable preservation of the digestive condition, which in itself was noteworthy; the freedom from pain when the functions of the stomach were taxed to their utmost, as in the digestion of a heavy meal of proteids; the existence of two unconnected cancerous ulcers in the stomach. Also noteworthy was the presence of a digestive leucocytosis with absence of a pathological increase in the number of leucocytes.

In view of the finding at the time of the second operation, and the post-mortem revelations—the practical limitation of the disease to the two cancerous ulcers—the condition noted by Dr. Keen and observed by others present at the time of the first operation seems quite inexplicable. The only attempt at an explanation is that there must have occurred during the whole time the stomach-wall was exposed a tonic contraction of this viscus, throwing it into folds, and thus originating the nodular condition simulating organic disease noted. Although this seems improbable, and it is, moreover, unlikely that Dr. Keen's years of anatomical and surgical experience, rendering him so familiar with the appearance of the healthy and diseased stomach, would have

permitted him to be deceived, no other explanation is at hand. For the fact remains that no evidence of gross or minute departure from the normal could be found to exist in the stomach-wall save at and immediately about the site of the ulcers. But if one with the extensive experience and keen powers of observation of the surgeon named could be so misled, not to speak of the others present who were similarly led astray, it indicates the extreme caution necessary in forming a judgment as to the condition of the stomach concerning presence or absence of a growth without an incision into that viscus.

The temporary entire subsidence of symptoms with decided increase in weight is occasionally noted after mere exploratory operation in cases of cancer of the stomach.[1] While temporary removal of symptoms after a gastro-enterotomy, in cancer producing obstruction of the pylorus, may be readily enough understood, the same after a mere exploratory section, if a causal relation can be traced, is in itself mysterious. I am unaware of any case similar to my own in which actual *apparent recovery* followed, the patient *remaining so long free from symptoms.* The explanation why a mere exploratory section, in which the involved organ is not disturbed, should be so promptly followed by cessation of symptoms and decided and long-continued general improvement in health as to indicate some relation between the operation and improvement, is not at hand. The quite common occurrence of marked amelioration in symptoms, if not actual removal of the disease-process, in tubercular peritonitis, following a mere exploratory section, is well known. Apparently, also, though it has been rarely noted, an extensive syphilitic gummatous formation in the liver may, without the employment of mercury or the iodides, be influenced in the same manner—as in a case reported by Stengel (see *Annals of Surgery*, June, 1897, discussion on Dr. Keen's paper). More frequently than the latter, but immeasurably less common than the former, are the observed cases in which so great an amount of symptomatic improvement has occurred following a simple cœliotomy in gastric cancer as to indicate the existence of a direct active rela-

[1] I speak here of *entire* subsidence of symptoms. I believe there is no authentic instance of total disappearance of all gastric symptoms with considerable gain in weight, the whole maintained for some months, in a case of well-developed cancer of the stomach treated medically. It is true that short periods of improvement often occur in cases under no special treatment, and that marked amelioration will often follow resort to the tube. But even in these last cases the symptoms never entirely disappear, nor is the gain in weight extensive or long held.

tionship between the operation and improvement. Yet these last are not known to be cases in which more than retardation of the growth was produced. We have no knowledge as to actual, partial, or complete disappearance of cancer of the stomach. It can only be said that such an occurrence is theoretically not impossible, if for no other reason, in view of the occasional observed disappearance of cancer of external parts, such as epithelioma, during the administration of full doses of arsenic. That in the case under observation a growth more extensive than was found post mortem had previously existed, the histological examination failed to reveal evidence. If carcinoma could be regarded as a germ disease, the likely explanation of cessation of growth and the occurrence of systematic improvement as the result of section in many cases of tubercular peritonitis, that of Kischenski, might be applicable here: that the result is due to a post-operative leucocytosis. If this were so, then it might be thought that the administration of nucleins would give similar results in cases of carcinoma in which there is yet at hand a fund of recuperative power. The nucleins, however, produce a physiological and not a pathological leucocytosis, the increase not being, as is usual in the latter, in the polymorphonuclear leucocytes, but, to a similar degree, in the young cells.

As factors assisting whatever gave the original impetus to the improvement in the case were the vigorous recuperative power presumed to be possessed by the patient, the well-preserved digestive function, and the freedom from involvement of the apertures of the stomach in the cancerous process. The character of the carcinoma, too, has to be somewhat considered. Although not the slow-growing form, such as scirrhus, adenocarcinoma is not supposed usually to tend to rapid metastatic extension. As was remarked by Dr. Adami[1] concerning this case, "columnar-celled cancers of the stomach are puzzling growths, in that of all forms of cancer of the stomach they appear to remain for the longest period purely local, and only infiltrate very slowly." If we do not consider the presence of the growths in the stomach, evidently but an isolated metastatis had occurred at the time of the first operation.

Although nothing in the microscopic or gross appearance of the

[1] In a private communication to Dr. Keen.

two growths permits the assertion that they were primarily simple peptic ulcers, which subsequently became carcinomatous, there is every probability that this is so, from the history and from our knowledge of similar cases, and from the fact that two identical separate ulcerating cancers were found. Whether the cancerous transformation of the ulcers was simultaneous or occurred serially, the second by infection from the first, is impossible positively to affirm. The latter is, of course, very probable. Infection by continuity of structure was scarcely likely, as was shown by the histologic examinations.

Infection may have occurred from contact through the occasional approximation of the two diseased surfaces of the empty stomach, the cancerous ulcer on the superior curvature near the cardia thus inoculating the simple ulcer on the inferior curvature; or particles of growth from the first, becoming dislodged, could easily have found their way to and a resting place on the site of the ulcer on the greater curvature. One might suppose that the very active digestive secretion, presumably always manifest in this case, would have tended to readily destroy the infecting principle before inoculation could occur. But we know too little of the intimate nature of this principle, or of its power of resistance, to hazard judgment on this point. At all events, the second ulcer was probably directly infected from the other cancerous ulcer. Other instances of presumed communicability of cancer are on record, such as epithelioma of the penis from coitus in a case of cancer of the cervix.

From the situation of the growths, encroachment upon the secretory power of the stomach did not occur; the stomach up to the time of death had practically normal function. Motility was somewhat interfered with, apparently not in consequence of the growths, but because of a slowly increasing pyloric hypertrophy with connective tissue increase, likely the result of the long-continued irritant action of excessive secretion of HCl.

The preservation of a digestive leucocytosis in this case, commonly but not invariably lost in cancer of the stomach, could not be a matter of surprise. Nor could it furnish to the thoughtful observer any valid evidence against malignancy, as the explanation for its preservation here is so evident. While the absence of a digestive leucocytosis is not in itself significant of cancer, commonly noted, as it is, in all maladies of the stomach in which peptonization of nitrogenous pabulum and its

passage into the bowel are interfered with, its presence has been held to point strongly against that affection. Recently some exceptions to the rule that a digestive leucocytosis is invariably absent in cancer of the stomach have been recorded. This is not a matter of surprise. It is rather a matter for wonder that it could be supposed that the condition for the absence of a physiological increase of leucocytes after a meal of proteids should be always the same in gastric carcinoma. With a growth involving the pylorus, especially if associated, as is usual, with a practical loss of secretion of HCl, absence of a digestive leucocytosis is to be expected. But, as in this case, with the preservation of the secretory power and fairly good motility, the ability to digest a full meal must have its usual effect upon the blood. It was more surprising that a pathological leucocytosis involving a notable increase in the number of leucocytes in the circulating blood was not evident in a case of cancer so long existing. Although a pathological leucocytosis is not as common in advanced cancer of the stomach as in cancer of other organs or parts, it is usually met with in fair degree except when the disease is in a situation to obstruct the cardia. It was especially interesting that, although an actual increase in the number of leucocytes had not occurred, a pathological leucocytosis was in reality actually present, showing itself in an alteration in the normal relation of the varieties to each other, the polymorphonuclear elements existing in the percentage of 79. Attention, I believe, is not enough given to the significance of the occurrence of a mere relative increase of adult cells in cases in which no increase in the absolute number existed. Here 79 per cent. of polymorphonuclear leucocytes in a subject lacking in vigor, if not attributable to the occurrence of blood oozing from the sites of the cancers (the only other, but unlikely, assignable cause evident), had its indication.

The diagnosis of a case of this sort is naturally attended with difficulty. The presence of carcinoma engrafted on an open ulcer, unless the latter has existed for a long time, has been often overlooked in life, so gradual is the merging of symptoms of cancer into those of chronic ulcer.

The diagnosis of these cases lies commonly in the recognition of a *carcinoma ex ulcere.* The ulcer has usually plainly enough preceded for a more or less long time the development of malignancy, producing the familiar characteristic symptoms. Not infrequently, however,

gastric ulcer is for a long time from the first latent. The usual symptoms may not be at all manifest. There may be practically no symptoms complained of, or those noted may be of a simple heightening in the secretion of HCl, or those of a gastric neurosis unassociated with hyperchlorhydria. The symptoms of presumed ulcer first remarked may then be really those of the developing cancer. The case under consideration was of this sort. During the six years symptoms were largely those of a pronounced neurosis associated with hyperchlorhydria. The gastric discomfort spoken of here was so explained, except that the uneasiness or pain occurring several hours after taking food, extending to the back, should have excited the suspicion of ulcer. No vomiting had occurred and no hemorrhage had been noted until six years had elapsed, during the whole period of which doubtless ulcer existed. The growth had then been present sufficiently long to produce a secondary distinct cancer in the stomach and a nodule in the omentum. In such a case as this, especially in the period following operation, the great improvement in the general condition, with the practical cessation of symptoms and the enormous gain in weight, would have made the diagnosis of carcinoma of the stomach very difficult. Even eighteen months succeeding operation, when the frequent appearance of coffee-ground material in the stomach contents, usually so strongly suggestive of cancer, was evident, other symptoms pointed so strongly against that condition, that its certain recognition was impossible, at least without the discovery of bits of the growth in the stomach-contents, here searched for, in the short time he was under observation, in vain. No doubt particles of the growth in a case of adenocarcinoma could eventually have been found had opportunity for any prolonged search been permitted. The diagnosis being regarded as settled from the knowledge of the character of the metastatic nodule, the finding of cancerous particles was not necessary.

In the diagnosis of a case of doubtful carcinomatous ulcer, apart from points mentioned, the following are also to be considered: the loss of weight and the cachexia, both apt to be out of proportion to what is usual in ulcer. The occurrence of constant oozing of blood, appearing as coffee-ground material in the vomit or in the wash water, is significant of cancer rather than ulcer. Also important is the lack of decided response to the improved methods of treatment

for ulcer, which usually rarely fail in prompt result in cases in which the lumen of the pylorus is not obstructed. Not long ago this, with the more or less constant presence of coffee-ground material in the vomit, led me to correctly diagnose carcinomatous degeneration in a case of chronic ulcer that had been under observation only a short time. The diagnosis was confirmed by finding a bit of the growth (an adenocarcinoma) in the wash water. The loss of weight may not be more marked than in ulcer, especially if the ulcer be so situated as to produce pyloric obstruction. The patient, also, may be very responsive to treatment for a time, as was true in the case just spoken of and in that of the subject of this paper. The extraordinary gain in the latter after the first section, with cessation of symptoms, could not but tend to mislead. Such a gain, long retained, however, is unknown as a result of any medical treatment of cancerous ulcer.

The general question of diagnosis of carcinomatous ulcer must be deferred for fuller consideration in a second paper, in which another case the writer has encountered and diagnosed in life will be described, as will be a case of chronic ulcer in a man of middle age, in whom adherent omentum caused the presence of a pyloric tumor suggestive of carcinoma. The present paper is intended merely as a report of what the writer regards as a remarkable case, worthy of isolated publication.

DISCUSSION.

Dr. W. E. Fischel reported the following case:

L. L., German, aged fifty-seven years, cooper, presented himself at the medical clinic of the St. Louis Medical College on November 7, 1896. Family history good; no hereditary taint. Both parents and paternal and maternal grandparents lived to be old. Patient's habits good, also previous health up to February, 1896. Has never had syphilis. Body weight, January, 1896, 141 pounds; February, 138; September, 106; October, 113. In February, 1896, he claims to have had an attack of dysentery, which incapacitated him for seven weeks, and caused a loss of twenty-three pounds in weight. He maintains that immediately following this attack he first noticed some disturbance of digestion. This continued up to the time he came for treatment.

A sensation of fulness after a heavy meal first attracted his attention to his stomach. This gradually led to occasional attacks of vomiting, which gave immediate relief to the distressing "weight" in his stomach. His desire for

food continues good, but the discomfort after eating is progressively increasing, a glass of water making him feel as uncomfortable as food. To relieve himself of the "uncomfortable stomach," he is in the habit of vomiting, forcing the act, within one hour after each meal. There is no complaint of pain. Soon after eating the patient belches a great deal, the eructations being usually acid. The extremities during this period are cold and clammy. The patient has a nervous countenance, is very thin, slightly anæmic, and expresses himself as feeling very weak. He declares, however, that he has improved in weight within the past few weeks.

The physical examination revealed no visceral lesion. The examination of the urine was negative so far as albumin, casts, and sugar were concerned.

The stomach-contents, expressed without reference to any special food taken, or time, were somewhat decomposed. The odor was offensive, and fragments of food (meat) taken twenty-four hours previous to examination were found in the contents. Phloro-vanillin test positive. Lactic acid absent. There was no gastric dilatation on inflation with air, the lower border of the stomach not extending below the level of the navel. On November 10th the patient took an Ewald breakfast, and after one hour the stomach was emptied. About 200 c.c. sour-smelling fluid was obtained, containing small fragments of poorly digested bread. Reaction acid; free HCl present, lactic acid absent. From the date of this examination up to within a few days of the time dissolution took place the patient's stomach-contents were examined at frequent intervals. Free HCl was always found present, lactic acid never present. Stagnated food was always found, but at no time did the inflated stomach extend below its normal anatomical confines. The patient progressively lost in strength and weight in spite of the fact that he did take food, and apparently digest most of it.

On December 5th, on inspecting epigastrium a small pulsating tumor is visible moving up and down with respiration. It can be felt as a small pulsating mass the size of a small hazel-nut, in the median line, half-way between the navel and xyphoid appendix. On January 5th, in this same region, a tumor can be felt, moving up and down with respiration, about as thick vertically as a finger and not quite an inch long transversely. It transmits the pulsations of the abdominal aorta. When the stomach is inflated (greater curvature reaching not quite to umbilicus) the tumor can be felt, but less distinctly than before. The patient was told of this tumor and an operation advised. This he refused to consider. The patient was put to bed and fed exclusively on cream, milk, and somatose. He took twenty-four ounces each of cream and milk in twenty-four hours, with one ounce of somatose. This amount of food did not give him any discomfort, and he seemed to assimilate it perfectly well. Notwithstanding this his weight on February 5th was only 102 pounds, a loss of eleven pounds in three months.

On April 7th, after having been confined to bed for three months, on the restricted diet of milk, cream, and somatose, the patient expressed a great desire for solid food. In my presence he ate with great relish a sandwich of

bread and butter and Swiss cheese. Much to the patient's surprise and mine, this agreed with him perfectly well, and from this time on he ate on each day plentifully of beefsteak, potatoes, turnips, corned-beef, cabbage, etc. Corned-beef and cabbage were particularly acceptable. I withdrew all former restrictions as to diet, and at the expiration of a week the patient visibly improved in appearance and strength. The examination of the stomach-contents showed, as before, the presence of HCl, total absence of lactic acid. There was some stagnation of food, but not more than is frequently found in an impaired digestion, be the cause what it will. The position and size of tumor about as reported under date of January 5th. The diagnosis of a gastric neurosis which was originally made, and had never been entirely surrendered, seemed now to be confirmed.

From April 7th the patient ate regularly some kind of solid food, together with large quantities of milk, cream, and somatose. He took twice a day one-drop doses of Calvert's carbolic acid, with one-twelfth grain doses of sulphate of morphia. This has been practically the only medicine administered during his illness. His condition, on the whole, continued to improve. There were times when the patient did not feel quite as comfortable after eating, but he never missed taking solid food three times a day.

On April 25th my notes record the tumor in the epigastrium very distinct, but it has not changed much in size or any in position.

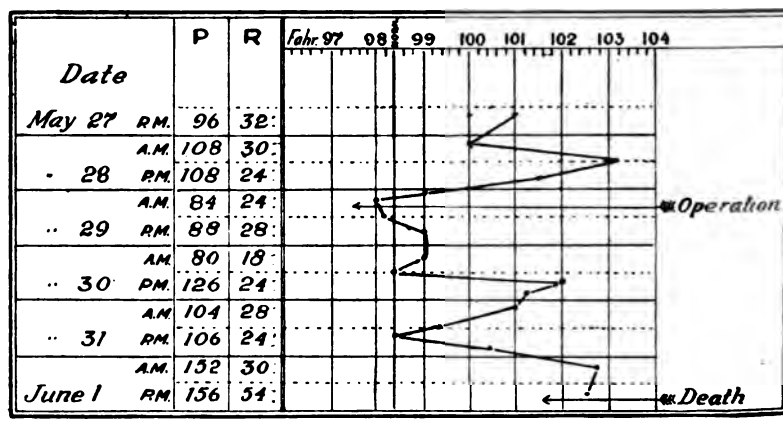
On May 20th the patient sent for my clinical assistant, because of suffering great pain. The pain began the day before, and remained almost constant. I saw him on May 21st. Patient can assign no cause for onset of pain. It is usually sharp and boring after eating; between meals it is more of a dull, aching pain. Appetite not so good as before, but patient can still eat solid food. He is afraid to eat much on account of pain. He looks very haggard, but this might be accounted for by his great suffering. The tumor has, however, increased in size, and now extends from median line to line dividing epigastrium from right hypochondrium. It is hard, extremely tender, and is about the size of a man's fist. Patient complains of a throbbing in the tumor. No vomiting or other symptoms of gastric disturbance. The rapid growth of the tumor, according to the patient's statement, dates from May 1st.

May 24th. Patient is still suffering greatly, and is taking no solid food, as this increases the pain. Tumor in epigastrium is exquisitely sensitive. Temperature 101.4° F. Pulse 120, feeble. He now for the first time is desirous of having an operation performed. On May 27th he was removed to St. Luke's Hospital.

May 28th. Patient had a restless night, but feels more comfortable this morning. He enjoyed his breakfast, consisting of tea, two soft-boiled eggs, bread and butter. This was not followed by any gastric disturbance. Milk, tea, and small quantities of bread were fed him at intervals up to 10 P.M. At 10 A.M. on May 29th he was removed to operating-room. He slept fairly well during the previous night, feels comfortable, but weak, which weakness he ascribes to want of food.

Before the abdomen was opened it was a question just what to look for. There could be no doubt as to the presence of a growth. The previous history of this case excluded the probability of the patient's having had at any time a gastric ulcer. A large number of gastric carcinomata, the carcinoma engrafted upon scar-tissue—ulcer scars—are recorded, in which HCl was always found in the gastric contents, even to the extent of hyperchlorhydria, as in Dr. Stewart's case. If this mass, which could now be well outlined, is carcinomatous, and I have no doubt of this, and involves the pylorus, then it is remarkable to have found, 1st, the constant presence of HCl in the gastric secretions; 2d, so little evidence of stagnation; 3d, no dilatation of the stomach; 4th, the very sudden rise of temperature of 103.4° F., as shown on the appended temperature-chart, with the exquisite tenderness involving the

FIG. 5.



growth, which in four weeks had grown to very large proportions. The occurrence of fever in gastric carcinoma is, on the whole, the rule, and usually indicates the beginning of the end. I do not remember, however, to have noticed in the literature of this subject any case in which the temperature came up so suddenly, and reached so high a point. I thought of an inflammatory process set up somewhere in the neighborhood of the neoplasm. An abscess of the liver was thought of. The absorption of a toxic material from the ulcerated area of the growth might account for the fever, but not for a temperature of 103.4°.

Dr. H. H. Mudd performed the exploratory laparotomy. A large tumor involving the pylorus and extending into the small curvature was found. This was too large and too adherent for a radical operation, and the patient not bearing the chloroform well, it was thought best not even to perform a gastroenterostomy. The patient died two days later, and the pathological specimen is here for your inspection.

You will permit me to read to you the notes made at the *autopsy*. The

body was opened eight hours after death. Except extreme emaciation and the abdominal wound, which was in good condition, nothing abnormal was noted externally. The abdomen alone was opened. There was no sign of peritonitis. The serous surfaces of the stomach and intestines were clean and smooth, and were not adherent to the abdominal wall. *The stomach was normal in size* and contained about 100 c.c. of a dark fluid. This did not give any blood reaction (hæmin test negative), nor could any lactic acid be detected with Uffelmann's test, even in the ethereal extract. No free HCl was present.

At the pylorus was situated a tumor about the size of a closed fist. There was distinct stenosis of the pylorus through which the little finger could not be inserted. Into the lumen of the stomach at the pyloric end projected numerous delicate cauliflower granulations. The lower third of the tumor *consisted of an abscess cavity not communicating with the lumen of the stomach.* Its contents were pus, with many cocci, chiefly staphylococci. The walls of the abscess cavity consisted of cancer tissue infiltrated with leucocytes. The cancer was of the medullary papillomatous type, the cells being numerous and cylindrical, the stroma slight and the blood-supply rich. *There was no sign of ulcer or of ulcer scar.* Near the lower margin of the stomach was a small gland indurated, but not carcinomatous. Liver, spleen, and other abdominal viscera were quite normal and contained no metastases. The abscess cavity filled with pus probably explains the sudden rise of temperature, and its presence embedded in a thick strata of carcinomatous tissue, not connected with the lumen of the stomach, makes this specimen particularly interesting.

DR. W. H. WELCH: I would like to say a word about the discrepancy of diagnosis in Dr. Stewart's case. Dr. Keen sent me sections from material removed for diagnosis at the first operation: one was of a lymphatic gland, and the other was of a small nodule said to have been removed from the omentum. The latter was typical carcinoma. Dr. Flexner and I found no reason to suspect anything else, the diagnosis seeming clear to us, and I was rather surprised to learn that the specimen had been called tubercular by a Philadelphia pathologist. Notwithstanding this discrepancy there seemed to me no real difficulty whatever in the microscopic diagnosis of the specimen, but the clinical course of the case led the physicians to feel sceptical as to the diagnosis. They had two reports, one saying that the specimen was tubercular, and another that it was cancerous. As Dr. Stewart has said, the patient, after the exploratory laparotomy, gained in weight, all the symptoms of cancer disappeared, he resumed his occupation, and for a time was thought to have completely recovered.

The most probable explanation of the presence of the multiple cancers in the stomach is that given by Klebs, that they are due to implantation rather than to metastasis. It is probable that one was an implantation-cancer rather than that there were two distinct primary growths.

The specimen sent me from the autopsy was in an advanced state of decomposition, and no staining of the nuclei could be obtained, but an adenocarci-

noma was, however, easily made out. Dr. Keen inquired especially as to the existence of diffuse cancer of the walls of the stomach. It seems that this diagnosis was, at the time of the operation, based upon a diffuse thickening of the stomach-wall, but it was not borne out by the microscopic examination. I judge that the diffuse thickening of the anterior wall of the stomach must have been due to contraction during the operation. There was no fibroid thickening and no infiltration extending far beyond the ulcerated growth.

DR. J. C. HEMMETER: It has been a great pleasure to me to listen to these very thorough clinical studies of the cases of gastric carcinoma and ulcer carcinomatosa. At Petzold's clinic it was found that the amount of hydrochloric acid increases much sooner in melano-carcinoma and lasts longer than in the scirrhous form. I believe, from what I have learned in conversation with Dr. Mall, of Hopkins University, that we can assume that the secretion of hydrochloric acid in any carcinoma is affected by the histological elements in the duct. I think that we can assume that the studies of Heidenhain and others are correct, and that the acid is manufactured in the border cells. If that is so, the degree of variance depends upon the intensity of the infection of the border-cells: as they will be variously invaded so will the secretion be affected. The explanation is not altogether hypothetical, but is based upon the statistics of Welch and others, who have shown that these ulcers have a predilection for the pyloric end of the stomach—that is, the end which secretes no hydrochloric acid.

In this interesting study of Dr. Stewart's, therefore, and in the report of the pathologists, I think the infiltration was not found to be very extended because of this, but was limited to that region where the peptic ducts do not secrete much hydrochloric acid.

DR. JAMES TYSON: I have a case now under my care that has been suggested by both of these cases. A man, sixty years of age, began to complain in October last of gastric symptoms that culminated in vomiting, with tenderness and pain. These symptoms were present when admitted into the hospital, probably eight weeks ago. He vomited an acrid matter invariably upon taking solid food. The frequent administration of an Ewald test-meal was followed in each instance by an abundance of free hydrochloric acid in the gastric contents, and the total acidity required often 6 c.c. of decinormal soda solution to neutralize it. A tumor was also located, and apparently remains. Somewhat to our surprise, on using a warm milk diet after admission, the man, although he had lost some forty pounds in weight since the beginning of his illness, began to improve, and goes now as long as two weeks without vomiting, and is gaining in weight. At no time was lactic acid found in the gastric contents after the test-meals.

DR. F. C. SHATTUCK: There was one remark in Dr. Stewart's paper which shows the peculiar workings of the surgical mind. Dr. Keen thought the

patient not well enough to have a stomach-tube used upon him, but that he was quite well enough to have his abdomen opened.

It is interesting to note the multiplication of cases of gastric cancer with persistent hydrochloric acid—a fresh illustration of the non-existence of a pathognomonic sign.

DR. W. W. JOHNSTON: Temporary improvement in cases of gastric carcinoma is so frequently observed that there must be some possible explanation for it. It has seemed to me that these cases are often due to improvement in the complicating catarrh. I can recall a recent case where a tumor was perceptible, with vomiting of everything taken; after complete rest of the stomach for ten days, the patient being fed entirely by the rectum, he improved so that he went back to solid food, ate that for a considerable time, and actually gained flesh and strength. Some of these cases of improvement are not difficult to explain in this way. It points, I think, to treatment that is not curative but beneficial, and which may for a time put these patients in in a better condition.

DR. STEWART: Of course, when I heard Dr. Welch's report I had no doubt that the case was one of cancer of the stomach, and so positively gave that opinion. As I remarked in the paper, it was not to be supposed that the two cancers had appeared simultaneously, but that one had in all probability produced the other.

I would suggest that it is worth considering whether a post-operative leucocytosis, which is a likely cause of amelioration of symptoms and recovery in cases of peritoneal tuberculosis, may not have been a feature in giving impetus to the improvement in this case.

There were no special indications of a gastritis accompanying the cancer in the case, and the diet he was put upon soon after operation should have aggravated such a condition had it existed. He improved in a marvellous way, reaching a weight of fifteen pounds more than he had ever weighed, and it all occurred so rapidly, with such a long period of cessation of symptoms, as to place the case a little out of the ordinary. I know of no similar one on record.

DR. F. P. KINNICUTT: The occasional improvement in cases similar to the one which has been described is difficult of explanation. Within the past two years two such cases have come under my observation. In both a large gastric neoplasm was present, and in one there was slight involvement of several of the peripheral glands. No particular treatment was instituted; the diet was such as the patients found easiest to take. In one case there was a gain of twenty pounds in four months, which has been maintained up to the present date, twelve months after the patient first came under observation. In the second case there was a gain of fifteen or sixteen pounds during six months, then rapid deterioration, and death after a few months.

DR. STEWART: That gain is a very moderate one. My patient ran up from 110 to 175 pounds, and I do not know of any case in which a gain like that has occurred.

DR. E. G. JANEWAY: I should like to speak of two cases of gastric cancer, in one of which, being pyloric, there was a gain of forty pounds. It was due to washing out of the stomach, and the trouble remained quiescent for four months. I would like to draw attention to another point; I have recently seen a case of carcinoma of the stomach commencing with hemorrhage. In this case, on account of severe hemorrhage, the patient was put on liquid diet, and kept on that for a time, and then, after three months, he was put on solid diet. He did better, the pain became less, and he gained some.

Another diagnostic sign that failed was the continued high hold of urea to the end. That is a point in diagnosis that has been alluded to. The autopsy showed a carcinoma two and a half inches in diameter, and in this case there was a persistent temperature for eight months, generally 101° F., sometimes 102° F. It is not necessarily a helpful point to regard the temperature; but the point I wanted to make was the continued hold of urea, the gain in strength, and the fact that in both cases the patients could take solid food better than liquid. In one of these cases the patient was always better when sitting up in bed. The carcinoma was in such a position, near the pylorus, that he complained invariably of pain in the back when he laid down.

DR. C. G. STOCKTON: It seems to me a rather significant fact that in instances of gastro-enterostomy, if recovery takes place a rather striking gain in weight is noticed, and it seems to me that may have some relation to the cases that are not operated upon. In other words, some of these cases may be explained by a condition of food-stagnation, with which there is almost always a decrease of weight. After food-stagnation ceases the patient gains again. I offer this as an explanation of the rather extraordinary transient gains in weight when undoubted carcinoma exists. Food-stagnation is sometimes temporary, and in its appearance and disappearance may have a marked influence upon general nutrition.

DR. A. H. SMITH: I would like to refer to a case that occurred to me three years ago. The patient had many of the symptoms of gastric malignant disease, but with the presence of hydrochloric and the absence of lactic acid, and his condition became so miserable that he was not able to be out of bed. It seemed as if his end was near. Suddenly, without any change in treatment, he began to improve, gained in weight, and strength got up, and was able to serve in the ward as an assistant orderly. He returned to his home in Connecticut, and for five months did fairly well, but again deteriorated and died. The autopsy showed the presence of gastric carcinoma.

DR. STEWART: I would say that a high urea output is to be expected in a case of this sort, in which the functions of the stomach were so well preserved, so that this could not furnish a link in diagnosis. I want again to emphasize that there was not merely a light gain in weight in my case, such as twenty pounds or more, but a gain of sixty pounds, and with entire cessation of symptoms for a period of about fifteen months; the case is, then, scarcely comparable with such as Dr. Janeway and Dr. Kinnicutt speak of.

ACUTE INTERSTITIAL NEPHRITIS.

By W. T. COUNCILMAN, M.D.,
of Boston.

Definition. An acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependent on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal.

This condition was first described by Biermer.[1] He finds the kidneys of a child four and a half years old, who died of scarlet fever, greatly swollen, the surface pale, and showing on microscopical examination intense infiltration of the connective tissue, with lymphoid cells. He considers the formation of lymphoid tissue here analogous to that found in typhoid fever. The cellular infiltration is more marked in the pyramids than in the cortex. E. Wagner[2] describes a similar case in which, however, the enlargement of the kidneys was not so marked. The consistency of the tissue is lax, the capsule easily removed, the cortex grayish-yellow, with punctate hemorrhages. There are accumulations of lymphoid cells in the interstitial tissue, most marked in the immediate vicinity of the glomeruli. In a subsequent article[3] he describes the condition under the name of acute lymphomatous nephritis, and considers it one of the four forms of acute Bright's disease. He finds this form of nephritis most often in scarlet fever, and sometimes in typhoid. The kidneys are greatly enlarged, brittle, the capsule easily stripped off, the surface covered with grayish-white elevations which correspond to streaks of cellular infiltration in the cortex. There are accumulations of round cells varying in size in the interstitial tissue. Some of these cells are smaller than leucocytes, others larger. The most acute cases of scarlatinal nephritis are of the lymphomatous form. In three typical cases which Wagner describes there was pharyngeal diphtheria in addition to scarlatina.

Klebs[4] gives a good description of acute interstitial nephritis. The kidneys are enlarged, of lax consistency, the capsule easily separated, the surface smooth and paler than normal. On section grayish-white nodules, corresponding to fatty degenerated convoluted tubules, are embedded in a rather transparent, gelatinous, grayish background. On microscopic examination the tissue between the tubules is dilated and filled with lymphoid cells. The cells come from the vessels. Letzerich[5] describes a kidney of this character in diphtheria, and regards the cells in the interstitial tissue as fungi. Coats,[6] in a case of scarlet fever in an adult, finds the kidneys enlarged and similar in appearance to the leukæmic kidney. The enlargement and pallor of the kidneys are due to infiltration of the cortex with round cells. These are packed between the tubules separating them, but not destroying the epithelium. The microscopical appearance closely resembles leukæmia. He afterward describes the cells in the interstitial tissue as due partly to proliferation of the interstitial cells, partly to emigration of leucocytes. The condition is common around the glomeruli in subacute nephritis.

Kelsch[7] regards acute interstitial nephritis as the typical lesion of the kidney in scarlet fever. He describes the cells as being of an embryonic character, closely packed together and often massed around the glomeruli. Klein[8 9] finds seven cases of well-marked interstitial nephritis in twenty-three cases of scarlet fever which he studied histologically. The interstitial cells are lymphoid in character; they vary in size, the nucleus is round, and two nuclei are often found in a single cell. The infiltration seems to take place first around the large vascular trunks at the base of the pyramids, and from here extends into the cortex. These cells compress the tubules, the epithelium becomes desquamated, and the lymphoid cells enter into the tubules. In these cases albumin is often absent, and there are no symptoms relating to the kidneys. He thinks that cases which die after the ninth or tenth day of the disease will, as a general rule, show more or less well-marked interstitial changes in the kidneys.

Phisalix[10] takes the ground that acute nephritis accompanying various infectious diseases, such as scarlet fever, is not a parenchymatous, but an interstitial process. In such cases but little change may be found in the parenchyma, while the interstitial tissue is dilated and filled with cells. Weigert[11] does not recognize acute interstitial

nephritis as one of the forms of acute Bright's disease. In the acute hemorrhagic form, he describes, in addition to the hemorrhages and epithelial degeneration, foci of brightly staining round cells in the interstitial tissue. He does not describe the character of the cells further, and considers the foci to be of an inflammatory character and secondary to the degeneration of the epithelium of the tubules and the destruction of the glomeruli. Waller[12] describes interstitial foci as common in post-scarlatinal nephritis. The cells are due to emigration, fibrous tissue may be formed from them, and a contracted kidney may be the final result of the process. Leyden[13] says that acute nephritis in scarlet fever and diphtheria is of a parenchymatous variety, but foci of small-cell infiltration are frequently found between the tubules and around the glomeruli. Bamberger[14] speaks of interstitial foci as common in the primary form of acute nephritis and in nephritis secondary to other diseases. Dunin[15] regards small-cell infiltration as one of the most characteristic changes in scarlatinal nephritis. The infiltration may affect the entire kidney or be limited to certain areas. These areas are most common close beneath the capsule or around the glomeruli. The epithelial changes may be slight, and there is no relation between epithelial degeneration and the interstitial foci. Fischl[16] finds in scarlet fever dilatation of the adventitia of the small arteries with round-cell infiltration extending from this into the tissue. In the cases of glomerulo-nephritis there is infiltration of the interstitial tissue most marked around those glomeruli which were most affected.

Friedländer,[17] in his description of scarlatinal nephritis, describes interstitial septic nephritis as one of the three varieties of scarlatinal nephritis. The kidneys in this are large, lax in consistency, the markings obscured, the cortex of a grayish-red opaque color, with foci of hemorrhage. The epithelium is but little altered, and the interstitial tissue contains numbers of small rounds cells. This form of nephritis he finds comparatively rare, occurring only twelve times in 229 cases, and is most apt to be seen in those cases of scarlet fever which are accompanied by diphtheritic septic processes. Cornil and Brault[18] find that acute interstitial nephritis is confined to the acute febrile diseases; they have met with it in scarlet fever and other processes. Nauwerk[19 20] describes in the kidneys, in both scarlet fever and diphtheria, foci of small-cell infiltration in the labyrinth and about the

small and medium-sized veins. The intertubular capillaries may be occluded by cells derived from proliferation of the endothelium. The cells in the interstitial tissue come from emigration, but may be added to by proliferation of the fixed cells. He finds no relation between these interstitial foci and epithelial degeneration.

Langhans[21] has never found a case similar to Wagner's lymphomatous kidney in scarlet fever, but has seen a slight degree of cellular infiltration in the walls of the small veins and around the glomeruli. Crooke[22] finds distention of the capillaries in the interstitial tissue by lymphoid cells and cells derived from proliferation of the endothelium of the vessels. In many cases foci of interstitial infiltration are found both in the labyrinth and close beneath the capsule. Litten[23] says that, apart from fatty degeneration and hemorrhage, the most common lesion found in the kidney in scarlet fever is the inflammatory round-cell infiltration of the interstitial tissue. Foci of this, consisting of closely packed leucocytes, are scattered through the entire kidney, varying in extent with the intensity of the process.

Oertel[24] in his work on diphtheria describes foci of round-cell infiltration both beneath the capsule and in all parts of the tissue. Cellular infiltration is also seen in the walls of the veins and arteries. There is no connection between the accumulations of cells and desquamation of the epithelium.

Sorenson[25] gives the clinical history and the pathological anatomy of a number of cases of scarlatinal nephritis, and among them three cases in which the interstitial lesions were well marked. In some of these cases there is a whitish opaque rim around the bases of the pyramids, with streaks extending from this into the cortex. V. Kahlden[26] gives a good description of interstitial nephritis in scarlet fever. He finds the cells in the interstitial tissue of unequal size, some smaller, some larger than leucocytes. In a case of diphtheria he finds numbers of cells in the vessels of the tissue between the cortex and the pyramids. These cells are round, in many cases twice as large as a leucocyte, the protoplasm homogeneous and transparent. The nuclei are round or sometimes indented, and two nuclei are sometimes seen in a single cell. These cells are more frequently found in the arteries than in the veins. Raginsky and Stamm[27] find in all the kidneys of scarlet fever cases who die in the first week of the disease more or less extensive interstitial infiltration with round cells. These cells

are either collected into masses simulating lymph nodules or are diffused over the entire cortex.

Bernhard and Felsenthal[28] find in diphtheria, along with degeneration in the epithelium, which they consider the principal change, foci of interstitial infiltration beneath the capsule around the glomeruli and in the upper portion of the pyramids. The veins are dilated and contain numbers of leucocytes. Aufrecht[29] gives the clinical history and pathological anatomy of three cases of scarlatinal nephritis which differ from the ordinary form in their early appearance and intensity. In all three cases there are masses of round cells, chiefly about the glomeruli. The changes in the parenchyma he considers independent of the interstitial lesions. Burmeister[30] describes interstitial foci in the kidneys of rabbits which are produced by the injection of chromate of ammonium into the circulation. There is no especial change in the epithelium of the tubules in the interstitial foci. He finds similar interstitial foci around the glomeruli in a case of glomerulo-nephritis in a tuberculous subject. Morse produced similar foci of cellular infiltration of the interstitial tissue of the kidney by injecting filtered cultures of staphylococcus aureus into the circulation of rabbits. Turner[31] makes two varieties of nephritis in scarlet fever, the glomerular and the interstitial hemorrhagic. In the glomerular type interstitial changes are often seen. Rosenstein[32] says the large interstitial kidney described by Friedländer is rare in scarlet fever, although even in cases of short duration, with albuminuria from the beginning, there is evidence of interstitial proliferation with focal accumulations of cells around the vessels.

Summing up these descriptions, I find acute interstitial lesions of the kidneys have been considered as common in scarlet fever, and regarded by some authors as constituting the most frequent pathological alteration of the kidneys in this disease. It has also been described in diphtheria and in other infectious diseases. The cellular infiltration of the interstitial tissue may be general throughout the kidney, with more intense foci in the cortex. In these cases the kidney is greatly enlarged, in some cases twice the normal size, the consistency is lax, and the section grayish and opaque. In other cases the infiltration appears as circumscribed foci either immediately beneath the capsule or around the glomeruli or at the bases of the pyramids. The cells in the interstitial tissue are almost universally described as

lymphocytes; in several cases their large size and the presence of two nuclei in a single cell are mentioned. Cell accumulations have also been described around the large vessels and infiltrating their walls. Von Kahlden describes in one case accumulations of large cells in the vessels in the pyramids. The cells have been generally considered as coming from the vessels by emigration. Almost all observers state that there does not seem to be any relation between foci of interstitial cellular infiltration and epithelial degeneration. There is general agreement that in scarlet fever the interstitial form of nephritis is most often found when the nephritis develops early in the disease, and is most common in the so-called septic cases. Many of the cases in which the most typical interstitial lesions were found are described as having diphtheritic pharyngitis. No evidence has been given by cultures that in these cases there was mixed infection with diphtheria.

The text-books on pathology do not devote much space to this condition. Most of the authors do not recognize acute interstitial nephritis as a special type of the disease. Others speak of foci of interstitial cellular infiltration as occurring frequently in acute and chronic nephritis. In many cases the cells in the interstitial tissue are regarded as pus-cells and the condition confounded with acute suppurative nephritis. Ziegler[33] has a very good description of the minor degrees of the process. In speaking of inflammatory œdema of the kidney he says: "The changes in the vascular stroma may take the form of circumscribed cellular infiltrations of the interlobular and circum-glomerular tissue, a condition of acute disseminated interstitial nephritis. The cellular infiltration makes its appearance in the neighborhood of the stellate and interlobular veins, and is usually so intense in these parts that in stained preparations the infiltrated patches are easily discernible under a low power of the microscope. The cellular aggregations are most numerous in the outer zone of the cortex and in the boundary zone between the cortex and medulla, the middle part of the cortex being seldom much affected." He says nothing of the character or origin of the cells, and thinks the condition may run a subacute course, gradually passing into the parenchymatous type.

The best description of the gross and microscopic condition in such kidneys is given by Orth.[34] He says:

"It is rare that œdema is the most essential inflammatory change in the interstitial tissue. I have often seen kidneys in which the tubules and glomeruli were normal and in which the only change consisted in a small-cell infiltration of the interstitial tissue. Such cases have been described as acute interstitial nephritis, as productive nephritis, as granulating nephritis, and as lymphomatous nephritis. These kidneys are more or less enlarged, softer, the surface mottled, of a grayish-red or grayish-white color, the markings cannot be distinguished. Such kidneys can be distinguished from those of acute parenchymatous nephritis by the absence of the markings and the cloudiness of the cortex. Microscopically there is an irregular distribution of cells between the urinary tubules. These cells have a round vesicular nucleus, they are not similar to emigrated leucocytes, and I regarded them as due to growth of the connective-tissue cells, although their frequent relation to the small veins would rather speak in favor of emigration."

I have previously[35] reported eight cases of this lesion in the kidney; three of these were from scarlet fever; two from diphtheria; one followed a criminal abortion, and two were of unknown origin. In all these the cellular infiltration of the interstitial tissue was the most marked, and in some cases the only change. Since then I have had the opportunity of examining microscopically the kidneys from a great many cases of diphtheria, scarlet fever, and other acute infectious diseases, and in the routine microscopic examination have found cases which showed every degree of alteration and most of which would have been overlooked without microscopic examination. The result of the further study of this important lesion in the kidney has thrown some light on the subject, and certainly caused me materially to change my views as to the origin of the cells in the interstitial tissue. In my previous communication I regarded the interstitial cells as derived from proliferation of the fixed cells of the tissue, particularly from the endothelium of the bloodvessels.

MACROSCOPIC CHANGES.

In the most marked cases the kidneys are greatly enlarged; in one case of diphtheria and measles in a child aged two years the combined weight of the kidneys was 480 grammes. In another child, aged eight years, with scarlet fever, the kidneys weighed 400 grammes; in two other cases of diphtheria, one in a child of five, the other in a child of two and a half years, the kidneys weighed 250 and 225 grammes. This extreme enlargement, which may be more than three times that of the normal, as in the first case mentioned, is

rare. In most cases the kidneys were but slightly if at all enlarged. The appearance varies. In the most marked cases the kidney presents an appearance which can be mistaken for nothing else unless it be the leucæmic kidney. The capsule is distended, thin, and easily removed, often separating spontaneously on section of the kidney. The fœtal markings are less distinct and often obliterated. The surface is pale, of a peculiar grayish-opaque color, somewhat resembling the amyloid kidney, mottled, with irregular more hyperæmic areas; the stellate veins of the surface are injected, often showing small punctate ecchymoses around them. In some cases the surface is irregular, due to the projection of small irregular nodules which are more opaque than the surrounding tissue.

On section of such kidneys the normal markings of the cortex are obliterated, and the contrast between pyramids and cortex is less distinct. The great increase in size is principally in the cortex, which may be three or more times thicker than normal. The glomeruli are not injected, and cannot be distinguished. The general color of the cut surface is grayish and opaque, with scattered areas of injection, and a few small scattered ecchymoses. Corresponding to the elevated areas on the surface, there are often areas more opaque than the general cut surface, which extend in lines from the pyramids through the cortex. At the bases of the pyramids the same opacity of the tissue is seen. The tissue of the kidney is soft, lax, and easily broken. It is very moist and an opaque milky fluid may be pressed out, and often flows from the cut surface. On scraping the tissue with a knife a milky fluid with small granular masses may be removed. In the less marked cases there is usually some degree of mottling, the cut surface is moist, and there are fine opaque lines or points. In many cases the changes are most evident at the bases of the pyramids and marked by a swelling and greater opacity of the tissue here. A very marked degree of change, as shown microscopically, may be present without producing macroscopic differences in the appearance of the kidney.

MICROSCOPIC CHANGES.

Sections of the fresh kidneys, to determine the presence of fatty degeneration, showed this change to be generally present, though in

slight degree. Fat was found in the epithelium of the tubules, and principally in the smaller collecting tubules. In a few cases foci of more intense fatty degeneration were found in the convoluted tubules. Occasionally a slight amount of fat was found in the interstitial tissue but not in the cells infiltrating this.

For microscopic examination thin sections of the tissue were hardened in Zenker's fluid, in corrosive sublimate, in alcohol, and in Flemming's solution. In general the best results are obtained after hardening in Zenker's fluid, and this was used in all of the routine examinations. The other solutions were used only in special cases and where the lesions were evident on microscopic examination. Various stains were used, the most satisfactory results being obtained by staining deeply with eosin, followed by Unna's alkaline methylene-blue solution.

In the most marked cases examination with low power shows the tubules widely separated and an intense cellular infiltration of the interstitial tissue. This is marked in all parts, but is more intense in areas. These areas are most often situated beneath the capsule and at the bases of the pyramids, and from these places the infiltration sometimes extends downward or upward. In the middle of the cortex there are also smaller areas of intense infiltration which seem not to be connected either with the areas beneath the capsule or with those at the base of the pyramids. In these areas the interstitial cells are closely packed together, with no intervals between them. Where the infiltration is less intense the cells lie singly in the tissue. Around all the glomeruli, but outside of the capsules, there seems to be more marked infiltration than elsewhere, save in the areas mentioned. In the pyramids the infiltration is often as intense as in the cortex, extending down to the pelvis.

With high power the cells in the interstitial tissue present a striking appearance. Most of them, and in some cases all of them, are of the same character. They vary somewhat in size and in shape. They are generally much larger than the polymorphonuclear leucocytes, and may be from two to four times the diameter of a red blood-corpuscle. Their shape varies: the single cells not in contact with one another may be round; but where they are packed together the shape is influenced by the mutual pressure. The nuclei present some variation in size, they are never vesicular, the periphery stains deeply,

and there are intensely stained points of variable size in the interior. The stained periphery often projects at certain points into the interior of the nucleus, and in most of the nuclei an intra-nuclear network connecting the brightly stained points within the nucleus and the points on the nuclear rim can be made out. The general body of the nucleus stains deeply. In most cases there is but a single nucleus in a cell. In others two or even three may be present. The nucleus occupies a very characteristic position. It is eccentric, and when the cells are elongated it lies usually at one of the ends. This eccentric position of the nucleus is sometimes so marked that it apparently projects from the protoplasm.

The amount of protoplasm around the nucleus varies. The most of the cells have a large amount while other nuclei are found with but little. The protoplasm is dense and often finely granular. In some of the cells the granulation is much more evident than in others. Even in the cells lying singly in the tissues the contour is not always sharp and round. In many cases both the cells here and in the masses have an irregular outline due to the protrusion of elongated and often knob-like masses of protoplasm. These present every resemblance in shape to leucocytes fixed while in emigration, and there is little doubt that these irregularities of form are due to amœboid movements. There is no appearance of a membrane around any of these cells. The most characteristic feature of these cells is the staining of the protoplasm. With most of the nuclear stains used singly the protoplasm stains faintly with the nuclear stain, but more intensely than the protoplasm of the epithelial cells. When stained with strongly alkaline methylene-blue the protoplasm stains deeply, and the blue color is preserved after counter-staining with eosin. A faint bluish tint, giving with the eosin a lilac tint, is often seen in the protoplasm of the epithelial cells, but in the interstitial cells the color is a deep blue. The cells can be instantly distinguished in a section, even with a low power, by their characteristic color. Nuclear figures are very numerous. As many as three or four are often seen in the field of an oil immersion. The cells in which the nuclear figures are found are large and have an abundant and distinctly granular protoplasm, the granules staining a deep blue.

These cells are found in the interstitial tissue. In all of the sections examined I have never found one of them within a tubule. In

the interstitial tissue they lie loosely in the spaces of the tissue, and a few are constantly found in the bloodvessels. They are not phagocytic; neither leucocytes, red blood-corpuscles, nor detritus of other cells are found inclosed in them.

In the very marked cases in which the kidneys are soft and enlarged other cells are constantly found in varying numbers in the interstitial tissues. The most numerous are cells corresponding to the lymphoid cells. The nuclei of these stain very much as do the nuclei of the large cells, and every gradation can be seen between the naked nuclei of the lymphoid cells and the large cells. Polynuclear leucocytes are usually present in varying numbers, depending on the degree of degeneration in the epithelium. In a few cases, especially where the lesions are very marked and the tissue disintegrated, I have also found cells of the epithelioid type in the interstitial tissue. These cells are, as a rule, larger, the protoplasm is finely granular, staining with eosin, the nucleus is less intensely stained than are the nuclei of the interstitial cells, and clearly vesicular. They can easily be distinguished from the blue-staining cells and there is no transition between them. These epithelioid cells, which are probably derived from proliferation of the tissue cells, are eminently phagocytic. I have found red blood-corpuscles, leucocytes, and in some cases the blue-stained cells inclosed within them. Nuclear figures are occasionally seen in the epithelioid cells, but never to the same extent as in the blue cells.

The epithelium shows various degrees of degeneration, and in places the tubules seemed to be actually destroyed.

The tubules are separated by wide areas of interstitial cellular infiltration, and often no tubules can be found in comparatively large areas. The slightest change found in the epithelium is a marked degree of cloudy swelling. In places the cells contain globular masses of hyaline, and the lumen of the tubule may be filled with the same material. In other cases the cells are swollen, vacuolated, and the greater part of the protoplasm may be lost, leaving only a small granular mass about the pale and rather shrunken nucleus. In places the tubules may contain desquamated epithelium or granular masses derived from this. The number of leucocytes present seems to depend upon the degree of destruction of the epithelium; they may be seen in the interstitial tissue, in the epithelial cells, and in the lumina of the

tubules. The glomeruli usually show no changes, although cases of typical glomerulo-nephritis may be met with in which acute interstitial nephritis is present as a complication. Granular coagulated material may be present in the capsular space, but even this is often absent.

In the less-marked cases the general diffuse interstitial infiltration is absent. A few scattered blue-staining cells may be found, but the lesions are eminently focal. In some cases the foci are so numerous that on holding a section to the light they appear as scattered blue specks or lines. Most of these areas, when observed with the naked eye or a very low power, are longitudinal in direction of the pyramids. In these foci the cells in the interstitial tissue are in great numbers, but not so numerous as in the foci in the most marked cases. These foci are principally found in three places in the tissue. As a rule, they are most numerous and largest at the bases of the pyramids, and from this point they may extend upward in the pyramidal extensions. Occasionally they are in large masses around the interlobular vessels. Next in frequency the foci are found beneath the capsule around the large branches of the stellate veins, which are often greatly dilated. Smaller foci may be found at various places throughout the cortex, but in the cortex they are most frequent around the glomeruli. The number of foci around the glomeruli varies greatly in different cases. In some there are cell masses around practically every glomerulus, in others only scattered glomeruli are affected. I have never found a case in which the interstitial areas were confined to the tissue around the glomeruli, but there were numerous cases in which the infiltration was confined to the bases of the pyramids or the subcapsular cortex.

These focal areas seem to stand in no relation to focal degeneration of the epithelium. In all cases degeneration of the epithelium is present. Where the infiltration is most intense there is apt to be extensive degeneration and even necrosis of the epithelium of the tubules, but this is probably secondary, and due to compression of the tubules and vessels. In these larger areas there are usually numbers of pus cells which may be found within the tubules. In the smaller areas no evidence of greater degeneration of the epithelium can be found than elsewhere in the kidney, and a high degree of degeneration may be found without any interstitial changes.

These changes in the interstitial tissue are always accompanied by

changes in the vessels. The interstitial cells are found in the vessels as well as in the tissue, and they may be so crowded in these and in the surrounding tissue that it is difficult to distinguish the vessels. Most of the cells in the vessels have the same character and the same peculiarity of staining as the cells outside. Nuclear figures are found in these cells, but not in such numbers as in the cells in the interstitial tissue. There are few polynuclear leucocytes among them. The numbers of cells in the vessels are not always proportionate to the numbers in the interstitial tissue. Vessels may be found blocked up with cells, with but slight interstitial change, and occasionally interstitial foci are found where but few cells can be made out in the vessels.

In making a systematic study of the kidneys in a large number of cases of acute nephritis special attention was given to the presence of these cells in the vessels. The vessels in which the greatest number of cells were found are always the branches of small veins in the upper part of the pyramid. In a large number of cases such cell accumulations were found in the vessels without any change in the interstitial tissue and without any more than the ordinary degeneration of the epithelium. In some cases all of the veins in this part of the kidney were so blocked up with cells that on holding a stained specimen to the light there was a decided blue color of the upper part of the pyramid. Such cell collections were occasionally seen in the stellate veins of the cortex and elsewhere, but in many cases they were confined to the veins of the pyramids. Most of these cells in the veins were of the same character as those in the interstitial tissue. The main difference between the cells in the vessels and those in the tissue was that the vessel cells were round and regular in shape. These cell accumulations in the vessels without interstitial lesions were found in 16 out of 103 cases of pure diphtheria; in 1 case out of 19 in pure scarlet fever; in 3 out of 23 in diphtheria and scarlet fever; in 2 cases of diphtheria and measles; and in 1 case of pyelo-nephritis, and in 1 case of acute endocarditis; in 24 cases in all.

There can be but one source for the cells in the interstitial tissue; they must come from the bloodvessels. In the first place, there are no cells in the tissue outside of the bloodvessels which could give origin to them. Practically the only cells which we have in the interstitial tissue of the kidney outside of the small collections of lymphoid cells, sometimes seen around the larger veins, are the cells of the

blood and lymphatic vessels. It is probable that there are cells belonging to the connective tissue, but it is difficult to demonstrate their presence. These cells in the most advanced cases in which there is actual destruction of the tissue do proliferate and mingle with the other cells in the interstitial tissue. The resulting cells are the epithelioid cells, and can be distinguished by the nucleus, the staining of the protoplasm, and their marked phagocytic properties, from the interstitial cells. Similar cells to the interstitial cells are found in the bloodvessels in the interstitial cases and in cases in which there are no interstitial lesions. It is impossible to see the irregular shapes and protrusions of the protoplasm of many of the cells in the interstitial tissue without being convinced of their amœboid properties. In a few cases similar changes of form were seen in the cells within the vessels, and in several instances such cells were found in the act of emigration, part of the cell being within and part without the vessel. The cells are principally confined to the vessels in the places I have mentioned. A few may be found in the larger veins, and they are occasionally seen in the vessels of the glomerulus.

The part which these cells play in pathology has received but little attention. Similar collections are most frequently described as small-cell infiltration, and no attention has been directed to their character and source. Unna was the first one who separated out from the cell collections in the interstitial tissue certain cells marked by a peculiar stain of the protoplasm, to which he gave the name plasma cells. Since then they have received considerable attention from the dermatologists and but little from pathologists. I consider the cells I have described in the interstitial tissue identical with Unna's plasma cells. Unna[36] describes in lupus cells whose protoplasm stained deeply with alkaline methylene-blue, and which do not decolorize as the other cells. He considers them identical with the cells described by Waldeyer as plasma cells, and gives them the same name. As these cells appear in the tissue the connective-tissue cells disappear, and he supposes that they are derived from the connective-tissue cells. In his first article on the subject Unna supposes that these cells were peculiar to the tuberculous process. He subsequently[37] describes the cells more fully, modifying his first description in several particulars. In this article he considers them as greatly hypertrophied connective-tissue cells. The blue staining is due to the presence of fine granules

embedded in the substance of the cell. He finds that they play an important part in the pathology of the skin diseases, and that certain new formations in the skin, to which he gives the name plasmoma, may be composed of them. The tumor cells in the round-cell sarcoma are derived exclusively from these cells, and they form the chief part of the cellular infiltration around other tumors. They are exclusively a pathological product, and are never found in embryonic or in normal tissues.

Jadassohn,[38] while confirming the presence in the tissues of the cells described by Unna, denies that they are solely differentiated from the other cells of the tissue by Unna's method of staining. He finds them in various inflammatory affections of the skin, and thinks they may be present in any form of acute inflammation with the exception of the suppurative. While he is uncertain about their origin, he denies that they are related to the connective-tissue cells.

Waldeyer at first believed that the cells described by Unna were identical with his plasma cells, but he afterward,[39] in an article on the cells of the connective tissue, declares that the latter belong to the group of mast cells, which are different from the cells described by Unna. He does not think the word plasma cell should be used to designate any of the connective-tissue cells.

Marschalkó[40] has written an important article bearing on the presence and origin of these cells. He finds them not only in various tumors and chronic inflammatory conditions, but also in acute inflammation produced by the injection of carbolic acid in the liver, and in acute suppurative inflammations produced in the subcutaneous connective tissue. They appear in the tissue within twenty-four hours, and are derived from the lymphoid cells of the blood. These accumulate in the vessels in the periphery of the inflamed area, pass through the walls, and change into plasma cells in the tissues. He lays more stress on the morphology of these cells, the character of the protoplasm and nucleus, and the constant eccentric position of the latter, than on any peculiarity of staining. He finds them in the vessels of the liver at a distance from the inflammatory focus and in the vessels of the spleen. He also finds them in small numbers in the spleen, lymph glands, and bone marrow. He makes the very important observation that after the injection of tuberculin their numbers in the vessels of the spleen are greatly increased.

Hodara,[41] working under the direction of Darrier, took up again the question of the presence of plasma cells in the normal tissues. He does not find them in the bone marrow, lymph glands, or spleen, in the normal embryo, child, or adult. He thinks that Marschalkó confounds the plasma cells with certain large mononuclear leucocytes, for which he proposes the name polyeidocytes, the name having reference to the variability of form which characterizes these cells. In some instances these cells may so resemble the plasma cells in size, form, character, and staining of the nucleus and protoplasm, as to be indistinguishable from them. In general the difference between the polyeidocyte and the plasma cell consists in the great irregularity of form of the polyeidocyte and the variability in form, size, and staining of its nucleus. The only other article of importance concerning the plasma cells is that of Justi,[42] who takes up the part which they play in the formation of the granulation tissue. Justi has included among the plasma cells large cells in the granulation tissue containing several nuclei. These cells are as much characterized by the character of the nucleus and protoplasm as by their manner of staining. Justi places the plasma cells among the leucocytes, and thinks they are derived from the lymphocytes.

It is perfectly evident that the cells we have described in the interstitial tissue and many of the cells in the cell accumulations in the bloodvessels of the kidney are the plasma cells of Unna. As to their origin I hold the same opinion as Marschalkó, that they are derived from the lymphocytes. In the kidney they enter into the interstitial tissue by emigration from the bloodvessels. They may emigrate from the vessels as plasma cells, or they may be formed from emigrated lymphoid cells. They have been seen in the act of emigration, and the shapes of many of the cells in the interstitial tissue can leave no doubt as to their amœboid character. A great part of those in the interstitial tissue come from proliferation. It is difficult to understand why previous observers of these cells should have been so uncertain as to their mitotic division, and should have found it necessary to resort to the very uncertain theory of multiplication by direct division of the nucleus. Nuclear figures are as numerous in the interstitial cells, and as definite considering their size, as will be found in a rapidly growing carcinoma. Certainly there is no difficulty in explaining the numbers of these cells met with in the kidney by emi-

gration and proliferation. Nuclear figures are also found in the cells within the bloodvessels, but not to the same extent as in the interstitial tissue.

With few exceptions, we have examined in every case of diphtheria and scarlet fever sections hardened and stained in the same way not only from local lesions, but from the liver, spleen, lungs, lymph glands, and bone marrow. A detailed account of these examinations will appear later. It will be sufficient to say here that in nearly every case of both diphtheria and scarlet fever, but particularly diphtheria, both those in which interstitial lesions in the kidney were marked, and where they were absent, great numbers of plasma cells are found in the spleen and bone marrow. They are also found in the lungs, liver capillaries, and lymph glands. The principal seat of their formation seems undoubtedly to be the spleen, where they are formed from the lymphoid cells. Sections of the spleen in some cases show nearly the whole of every Malpighian body converted into plasma cells. Groups of them were also found in the pulp of the spleen and in the vessels. In all these places there are numerous nuclear figures. It is not probable, as Unna assumes, that direct nuclear division ever takes place in these cells. In the bone marrow, which is red in nearly every case, numerous groups of plasma cells are also found. In the lungs they are found in great numbers in the bloodvessels, but especially in the connective tissue of the lung around the bronchi and bloodvessels. In places they play an important part in the cellular exudation in the focal pneumonia, but are found principally in the vessels and interstitial tissue, rarely in the alveolar exudation. In the lymph glands, save in those in the immediate vicinity of the throat lesions, they are much less numerous than in the spleen and bone marrow. In the liver they are in the capillaries, and probably come there from the spleen. Sections from the larger bloodvessels containing blood, and of decolorized blood-clot from the heart, are not so satisfactory for examination as the tissues, but they are found here in small numbers.

Investigations are now in progress to determine the presence and numbers of these cells in the peripheral circulation in cases similar to those in which they are found in the tissues.

With regard to the presence of the plasma cells in normal tissues, it is remarkable that those investigators who have taken up this ques-

tion should have left out of consideration the organ in which they are always present in enormous numbers. In the alimentary canal, from the stomach to the anus, all the cells of the tissue between the epithelium and the muscularis mucosa are practically plasma cells. They are comparatively rare in the follicles in this region.

In the tissues examined for fatty degeneration, both by fresh section and after Flemming, there is no fat found in the plasma cells. Evidence of cell necrosis, as shown by nuclear detritis, is not found in them. The only evidence of degeneration which may be found in the plasma cells, both in those in the interstitial tissue and in those in the bloodvessels, consists in the presence of vacuoles in the cells, or hyaline droplets which occupy the same position as the vacuoles, and which often stain homogeneously with methylene-blue.

We are led to the belief that the plasma cells have their origin in the lymphoid cells from the similarity of their nuclei to those of the lymphoid cells, and from the presence of transitional forms between the lymphoid and plasma cells, as shown by the gradual accumulation of protoplasm of the same character as that of the plasma cell around the nucleus. This does not take place evenly around the nucleus, but always at one side. The constant eccentric position of the nucleus of the plasma cell is one of the most marked characteristics of the cell.

In the examination of the kidneys of the autopsies in the last two and a half years I have found 42 cases of acute infectious diseases in which acute interstitial nephritis was present. The service in the hospital is an acute one, and there are comparatively few autopsies on chronic cases. All of the cases in which interstitial infiltration with plasma cells was found are included in the 42 cases. Those in which lymphoid cells were found around the large interlobular veins are not included. The majority of the interstitial cases come from the acute infectious diseases of children, which make up a large part of our autopsy material. In 103 cases of pure diphtheria a varying extent of interstitial change was found in 24. In 20 cases of pure scarlet fever interstitial lesions were found in 5. In 23 cases of mixed infection of diphtheria with scarlet fever, interstitial nephritis was found in 5, and in 2 out of 5 cases of diphtheria and measles. The other diseases in which the lesion was found were measles and whooping-cough, 1; empyema, with subsequent diphtheria infection, 1; lobar pneumonia and pericarditis, 1; epidemic cerebro-spinal meningitis, 1; lobar pneumonia,

1; acute glomerulo-nephritis, 1; acute endocarditis following abortion, 1.

Acute interstitial nephritis is far more common in the infectious diseases of children, and is occasionally seen in other acute infectious diseases. This fact and the focal character of the lesions suggest at once the agency of bacteria. The general diffuse degeneration of the epithelium which was so constantly found is evidently to be referred to the action of some soluble toxic substance. The results of the bacteriological investigation, both by microscopic examination of sections stained for bacteria, and by cultures of the organs made at the autopsies, have not borne out the bacteriological theory. In all cases cultures were made at the autopsies of the primary lesions of disease whatever its character—of the blood, lungs, liver, kidneys, and spleen. The results of the cultures of the kidneys in the 42 cases of interstitial nephritis were as follows: In 24 cases of pure diphtheria the kidney was sterile in 6. In 11 the colon bacillus was found; in 1 case the staphylococcus aureus; in 5 cases the streptococcus pyogenes; in 8 the diphtheria bacillus, and in 1 the bacillus fœtidus. In the 5 cases of pure scarlet fever the colon bacillus was found in 2, the streptococcus in 3, and the staphylococcus in 1. In the 8 cases of mixed infection of diphtheria with scarlet fever or measles 2 were sterile; in 3 the streptococcus, and in 3 the colon bacillus was found. In the other 6 cases the colon bacillus was found in 3; the staphylococcus aureus in 2; the streptococcus pyogenes in 4; the pneumococcus in 1, and 1 case was sterile. I have included the colon bacillus in the result of the bacteriological examination, although I am not inclined to regard the presence of this as determined by cultures made at the autopsy as a matter of much etiological value. Bacteriological examinations of the kidneys in the same diseases, but in which interstitial lesions were not present in the kidneys, have shown the same results. The kidneys were sterile or the same organisms were present in about the same proportion. It is obvious from this that we cannot lay any weight on the presence of bacteria in the kidneys as a causative factor in the acute interstitial lesion.

In seeking an explanation of the focal character of these lesions their situation must be taken into account. They are most marked, first, in the boundary zone of the pyramids; second, beneath the capsule; and third, around the glomeruli. There can be but two ex-

planations for the presence of these foci. Cells are brought to the foci by the vessels, they emigrate from the vessels into the interstitial tissue, but probably the greater part of those in the interstitial tissue come from proliferation. Either there must be some physical condition in the circulation which may account for their accumulation in the vessels, or there must be some substance in the tissues which exerts a positive chemotaxis for just these cells, and which causes both their accumulation in the vessels and their emigration into the tissues. There is much which seems on purely physical grounds to favor the accumulation of cells in the long veins of the pyramids. These veins are long, they are numerous, and the circulation in them is slow. It is possible that the large cells in the circulating blood might be mechanically retained in these vessels. Weight is given to such a supposition from the fact that even small substances in the circulating blood may be mechanically retained here.

The hæmatogenous abscesses of the kidney, both those produced experimentally and those seen in man, are more apt to be formed in the upper part of the pyramid than elsewhere in the kidney. The organisms for the most part pass through the capillaries of the cortex; they become attached to the walls of the veins, and increase there, finally occluding the vessel and producing necrosis in the surrounding tissue. The presence of large numbers of these cells without any emigration speaks in favor of such a mechanical theory. The same thing would hold true, though to a less extent, in regard to the cell accumulations in the stellate veins. Occasionally the cells are seen here without interstitial lesions, but to nothing like the same extent as in the pyramidal vessels. Nuclear figures are found in the cells within the veins. The cells can pass through the vessels into the interstitial tissue, and the same conditions which led to their production and proliferation in the first place could cause them to proliferate in the interstitial tissue. Tumor cells can act in this way, and there is certainly some temptation to regard the interstitial foci very much in the same light as tumor metastases.

Such a mechanical theory fails to explain the interstitial foci around the glomeruli. Occasionally a few cells may be found in the vessels of the glomeruli without any interstitial lesions. Not only do periglomerular foci speak against the mechanical theory, but these cells are not found to the same extent in the vessels elsewhere, even in

organs where the conditions of the circulation would seem to favor their presence. A few are almost constantly found in the capillaries of the liver, but their production in the spleen would explain this. They are found in the vessels of the spleen and bone marrow, and in both of these places they are evidently produced. On the other hand, assuming that their presence in the kidney is due to some substance which exerts a positive chemotaxis for them, there are equal difficulties in an explanation. They are not attracted by simple degeneration and necrosis of tissue, as are the polynuclear leucocytes, and are not simply secondary to epithelial degeneration. Dr. Morse in a study of cantharidin poisoning (not yet published) has shown most extensive degenerative lesions, and even necrosis, without any change in the interstitial tissue and without leucocytes.

Ribbert[43] has recently published an interesting article in which he endeavors to explain the focal accumulation of cells in the kidney. In this article he calls attention to the locality of the foci of cellular infiltration and atrophy. He finds in chronic nephritis the lesions in the same situations which I find in the acute interstitial process. Ribbert explains this localization by the degeneration produced in the irregular tubules (Schaltstücke) by the concentrated toxic urine, and by the toxic urine passing directly through the thin capsules of the glomeruli. The pyramidal lesions are due in part to the toxic action of the urine in the collecting tubules, and in part to toxic substances which have passed into the tissue, passing along the lymph spaces to the large lymphatics in the boundary zone. It is possible that the general degeneration of the epithelium which we find in these cases may be due either to the toxic qualities of the urine or to the blood. The interstitial lesion may be due to some substance excreted by the kidney, the foci being determined either by the action of this material where it becomes more concentrated, or where it escapes into the tissue, or the paths which it takes in the tissue. It is possible that the physical conditions of the circulation in the kidney may play a part, and possibly an important part, in determining the foci.

But little is gained from the clinical study of these cases. There was albumin in the urine, as there is in all cases of diphtheria. In none of the cases was there marked diminution in the amount of urine and in none was there œdema. There was apparently nothing in the clinical history of the cases which called especial attention to the

condition of the kidneys. In the literature of the disease there are some cases in which the clinical history is given. In Biermer's case, the disease being scarlet fever, the renal symptoms began two weeks before death, with marked diminution in the amount of urine, and dropsy followed by uræmia. In 3 cases of acute lymphomatous interstitial kidney in scarlet fever which Wagner reports, 1 died on the tenth and 2 on the seventeenth day of the disease. All 3 of the cases had pharyngeal diphtheria. Klein found the condition most frequently in those cases of scarlet fever which died after the ninth day of the disease. Friedländer found the lesions which he describes as interstitial septic nephritis in those cases of scarlet fever which are accompanied by severe diphtheritic septic processes.

The disease has a rapid course, and normal urine may be seen even twenty-four hours before death. Usually there is no œdema. It is probable that the 12 cases which Friedländer described, and which were from 229 autopsies on scarlet fever, represented marked types of the disease in which the lesions were evident macroscopically. Had he made systematic microscopic examinations he must have found minor degrees of similar lesions much more frequently. Sörensen gives the clinical histories of 3 cases. He also says the interstitial form is most common in cases of severe diphtheritic septic scarlet fever, and appears early in the disease. In one of his cases there was slight œdema and ascites.

In addition to these 42 cases, in which the interstitial lesions of the kidney were due to a general disease, 3 cases were found in which the interstitial process was due to the local action of bacteria.

The first case was one of ascending ureteritis and pyelonephritis. The kidneys were enlarged, weighing 390 grammes (small, slender woman), injected, somewhat œdematous, and on section whitish-yellow streaks in the cortex extended from the bases of the pyramids toward the capsule. The tissues in these areas of infiltration were not softened. Cultures from these areas gave colon bacilli and a few colonies of streptococci. On microscopic examination of sections in some of the larger areas there was a mass composed of necrotic tissue and filled with nuclear detritus. There were small areas where the necrotic tissue seemed to have been composed of pus cells, but for the most part the remains of the cells and nuclei seemed to have come from large cells. In the periphery of the larger foci, and in the whole

extent of the smaller, there was intense infiltration of the tissue with plasma cells. Sections from the ureter and pelvis of the kidney showed slight superficial necrosis, comparatively few pus cells, and great numbers of plasma cells. Plasma cells were found in the vessels in the neighborhood of the foci.

The second case was one of hæmatogenous abscesses of the kidney following carbuncle of the neck and thrombosis of the lateral sinuses. The kidneys contained numbers of small abscesses, which were most numerous in the boundary zone of the pyramids. Cultures showed a general infection with staphylococcus aureus. Sections showed typical metastatic abscesses with masses of large micrococci in the centre, and around these a mass of pus cells with much nuclear detritus. In the tissue on the outside of the abscesses there were numbers of large epithelioid cells which often contained micrococci and other cells inclosed in them. Outside of these there was extensive infiltration with plasma cells. Plasma cells were found in the vessels.

The third case showed both processes, a general interstitial nephritis and small abscesses with surrounding infiltration with plasma cells. This was from a case of scarlet fever complicated with extensive abscess formation beneath the scalp. Cultures showed a general staphylococcus infection.

In all three cases the spleen was enlarged, and on section showed large numbers of plasma cells in the tissue.

SUMMARY.

Acute interstitial nephritis is found in the infectious diseases of children, particularly in diphtheria and scarlet fever, but may be met with in other infectious diseases.

The disease is characterized by general and focal infiltration of the interstitial tissue of the kidney with cells which correspond to those which Unna has described under the name of plasma cells. The focal character of the infiltration is marked; even in the cases in which all parts of the kidney show some interstitial cellular infiltration the cells are most abundant in certain foci. These foci are found in three places: in the boundary zone of the pyramids, in the subcapsular region of the cortex, and around the glomeruli. A considerable number of cases is found in which the bloodvessels of the

boundary zone of the pyramids contain numbers of lymphoid and plasma cells without any infiltration of the interstitial tissue. The new cells in the interstitial tissue are due to emigration from the bloodvessels and multiplication by mitotic division of the cells which have emigrated. The cells can emigrate as plasma cells or as lymphoid cells, and the latter may change into plasma cells in the tissues. In the normal individual plasma cells may be formed in the mucous membrane of the intestine, where they practically form the entire tissue between the epithelium and the muscularis mucosa, and to a limited extent in the spleen. In diphtheria, in scarlet fever, and probably in a number of infectious diseases, plasma cells are formed in great numbers in the spleen and bone marrow, and to some extent in the lymphatic glands. In the spleen they are formed from the cells of the Malpighian bodies, which are often principally composed of them, and to some extent from the cells in the pulp. They are formed from the lymphoid cells.

No adequate explanation is found for the focal character of the lesions in the kidneys. There is some ground to believe that the physical conditions of the circulation may have something to do with their accumulation in the vessels in certain places. It is also possible that in the interstitial foci there may be soluble substances which exert a positive chemotaxis for them. Such substances may be found in the urine, which may exert its influence on the interstitial tissue in different places. The explanation of the foci cannot be found in primary focal degeneration of the epithelium. Epithelial degeneration in these cases is always present, but it is diffuse. In foci where it is more intense and due to the interstitial changes polynuclear leucocytes are found in the tissue in the degenerated epithelium and in the tubules. Polynuclear leucocytes and not plasma cells are attracted by degenerated tissue. The foci are not due in these cases to the local action of bacteria.

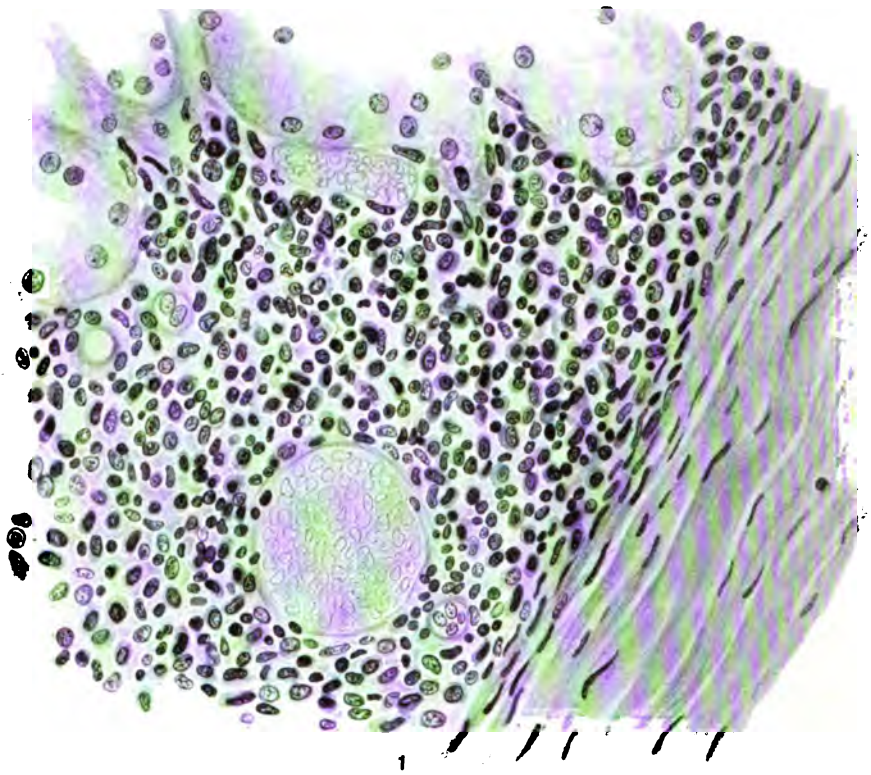
In a number of the cases in which interstitial nephritis was found the kidneys were sterile both on cultures and microscopic examination. In cases where bacteria were present they were found only in small numbers in cultures and not on microscopical examination, and their connection with the foci could not be demonstrated.

In three cases plasma cells were found in the interstitial tissue in definite bacterial diseases of the kidney. In these cases they were

not found in connection with the lesions produced directly by the bacteria, but in the periphery of the purulent foci.

BIBLIOGRAPHY.

1. Biermer. Virchow's Archiv, 1860, xix. 537.
2. Wagner. Arch. d. Heilkunde, 1867, 263.
3. —— Deutsch. Arch. f. klin. Med., 1880, xxv. 529.
4. Kleba. Handbuch d. path. Anatomie, Berlin, 1876, Bd. i p. 632.
5. Letzerich. Virchow's Archiv, 1871, liii. 324.
6. Coats. British Medical Journal, 1874. 401.
7. Kelsch. Arch. de Physiol. Norm. et Path., 1874.
8. Klein. Loc. Gov. Report, London, 1875.
9. —— Transactions of the Pathological Society, London, 1877.
10. Phisalix. Paris Thesis, 1877.
11. Weigert. Volkmann's Sammlung, 1879, Nos. 162, 163.
12. Waller. Journal of Anatomy and Physiology, 1880, xiv.
13. Leyden. Zeitschr. f. klin. Med., 1881, iii.
14. Bamberger. Volkmann's Sammlung, 1882, No. 173.
15. Dunin. Virchow's Archiv, 1883, xciii. 287.
16. Fischl. Zeitschr. f. Heilkunde, 1883, iv.
17. Friedländer. Fortschr. d. Med., 1883, i.
18. Cornil and Brault. Etudes sur la pathologie du rein. Paris, 1884.
19. Nauwerck. Ziegler's Beiträge, 1886, i.
20. —— Deutsche med Wochenschr., 1884.
21. Langhans. Virchow's Archiv, 1885, xcix. 193.
22. Crooke. Fortschr. d. Med., 1885, iii. 651.
23. Litten. Charité-Annalen, 1882, viii.
24. Oertel. Die Pathogenese d. epidem. Diphtherie. Leipzig, 1887.
25. Sörensen. Zeitschr. f. klin. Med., 1891, xviii.
26. v. Kahlden. Ziegler's Beiträge, 1892, xi.
27. Baginsky and Stamm. Arbeiten a. d. Kinderkrankenhause, Berlin, 1893.
28. Bernhardt and Felsenthal. Arch. d. Heilkunde, 1893, xvi.
29. Aufrecht. Deutsches Arch. f. klin. Med., 1894, lii.
30. Burmeister. Virchow's Archiv, 1894, cxxxvii.
31. Turner. Guy's Hospital Reports, 1894.
32. Rosenstein. Pathologie d. Meierkrankheiten, 1894.
33. Ziegler. Lehrbuch, 1893.
34. Orth. Lehrbuch, 1893.
35. Councilman. Medical and Surgical Reports of the Boston City Hospital, 1897.
36. Unna. Monatsch. f. prak. Dermatologie, xii. 296.
37. —— Berl. klin. Wochenschr., 1893, 240.
38. Jadassohn. Verhandl. d. deutschen dermatol. Gesellsch., II. Congress, 1891.
39. Waldeyer. Sitzungsber. d. Berl. Acad. d. Wissenschaften, 1895, xxxiv.
40. Marschalkó. Arch. f. Dermat. u. Syph., 1895, xxx.
41. Hodara. Monatsch. f. prakt. Dermatol., 1896, xxii.
42. Justi. Virchow's Archiv, 1897, cl.
43. Ribbert. Virchow's Archiv, 1897, cl.



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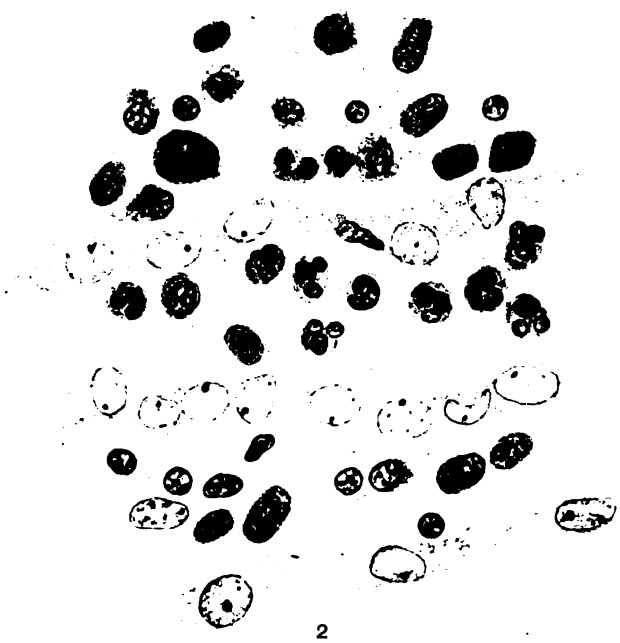

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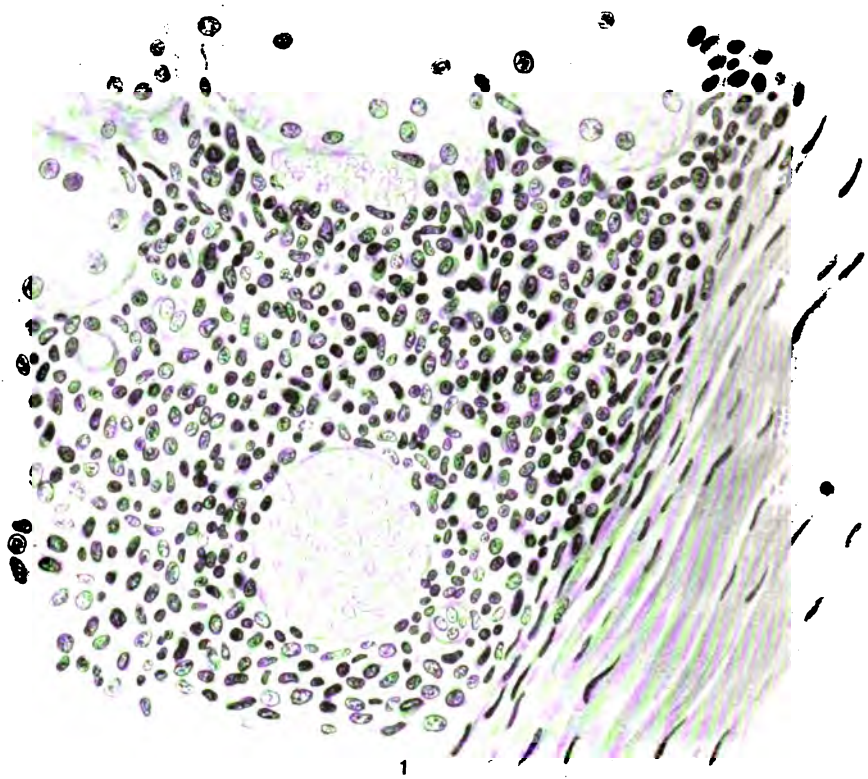
COUNCILMAN.—Acute Interstitial Nephritis.



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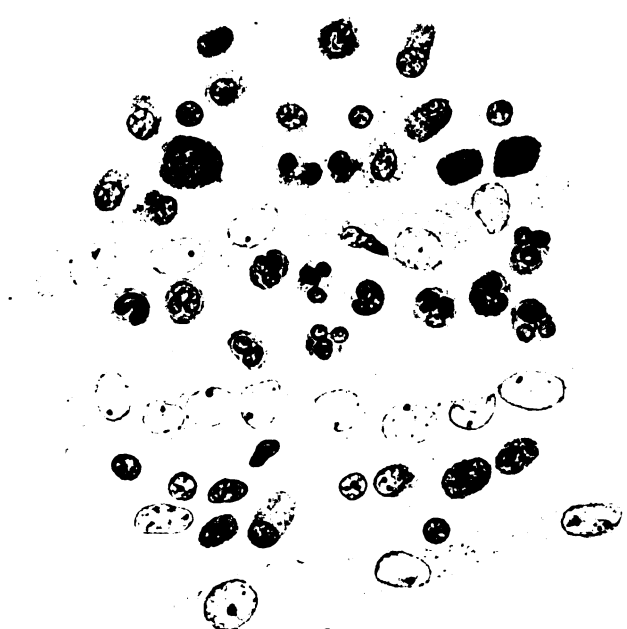


2

COUNCILMAN.—Acute Interstitial Nephritis.

SEPTIC PERFORATION OF THE RIGHT INTERNAL CAROTID ARTERY.

Autopsy Five Months after Death.

By A. JACOBI, M.D.,
AND
JAMES EWING, M.D.,
OF NEW YORK.

The clinical history of the case, which was learned five months after death, began two weeks before death with ordinary symptoms of croupous tonsillitis; there were membranes on both tonsils. The report of the New York Health Department gave no Klebs-Loeffler bacilli. After one week the throat was pronounced clear and the child was much better. Monday, May 2d, about one week after the beginning of the illness, the patient had a severe chill, with rise of temperature, pain in the throat, and dysphagia. The lymph nodes on both sides of the neck soon became much swollen. The temperature rose considerably and the patient was much prostrated. On May 4th there was a considerable hemorrhage from the nares and pharynx. On May 6th a second very profuse hemorrhage occurred, "filling a bowl" with apparently arterial blood. Its color was described as being bright. On May 8th there was a third severe hemorrhage; the nares were then plugged. On May 10th, early in the afternoon, the plugging was removed from the nares while the child was struggling much, and a fourth severe and fatal hemorrhage occurred, blood coming from the nose and mouth. The exact point of issue of the previous hemorrhages was not ascertained.

The *autopsy* was held five months and eight days after death, October 18th. The body had been interred in dry gravel, in a wooden casket surrounded by a casing-box of pine. The outer box was quite dry. The casket was moist, with no moulds seen inside or out. Running from the foot of the casket was a blood-stained line which had slightly soiled the covering of the coffin and the bottom of the box. The internal coverings were moist, the clothing of the cadaver much decayed in places, especially over and under the trunk. Covering the clothing and the skin of the entire body was a layer of coarse, brownish dust, in which were many small white insects the size of a pin-head, and their small oval eggs. This dust, composed of the insects and excreta,

had produced a dark-brown discoloration of the skin, especially of the face, which was nearly black in places.

The body was rigid, the skin much desiccated, and over the fingers almost horny. The nails and hair were firm, the teeth very loose. The orbits contained a little black, grumous fluid; the lids and lashes were intact. The cheeks, chin, nose, and features were apparently natural and not shrunken.

The tissues of the neck were more moist than elsewhere. Over the right parotid, the sternomastoid, and in the posterior temporal region there was marked œdema of all the tissues. The lymph-nodes of both sides of the neck were much swollen down to the clavicles. The tissues of the posterior pharyngeal walls were very dark but not necrotic, especially on the right side. A large cavity, filled with black fluid in one compartment and bright blood in the deeper portions, was found bounded internally by the right tonsil and pharyngeal wall, which here was very thin; it reached about 2 cm. below the tonsil, above nearly or quite to the bony vault of the pharynx, and it extended posteriorly to the deep tissues of the neck and involved the internal carotid and its branches in their irregular ramifications. This cavity consisted of one older, smooth-walled portion lying nearest the tonsil and just behind the thinned pharyngeal wall, and measured about 2 cm. in diameter. The rest of the cavity appeared to be of more recent formation, and was filled with fresh blood, partly clotted. The internal carotid, 1.5 cm. above its origin, showed an irregular opening, 5 mm. in circumference, freely communicating with the deeper portion of the above cavity. On the posterior wall of the pharynx, at the level of the tip of the epiglottis, was a ragged opening of similar dimensions, leading into the older and superficial portion of the cavity. The tonsils showed numerous deep excavations but no ulcerations. The mucous membrane of the nares was in an advanced state of decomposition, the periosteum was loose, the vomer free from its articulations; there were no evidences of hemorrhage in this region. The larynx appeared quite normal, but was filled with reddish-brown fluid. The trachea was normal.

The lungs were very firm, the pleura desiccated and shiny. There were four ounces of yellowish, transparent fluid in the pleural cavities. The lungs showed numerous lobules sharply marked off, dark-reddish, filled with blood. In the right lower lobe one area was softened, gelatinous, decolorized, resembling clots found in some veins. The lungs otherwise were very anæmic.

The heart was very hard and tightly contracted. The right side contained a firm, dark clot of moderate size; the left was entirely empty. The muscle, though anæmic, was normal; its valves were normal.

The liver was much desiccated superficially and very firm; very light leaden in color. The markings were indistinguishable. Section showed numerous small cavities, some of which are patent bloodvessels. The gall-bladder was contracted and empty. The spleen was moderately enlarged, the capsule smooth, hard, and dry: it was dark-gray on section. The Malpighian bodies were light-gray and very distinct.

The kidneys were normal in size, very firm in consistence, and dry. On section, they were light-colored and anæmic. The pyramids were moderately congested, the markings distinct and regular. The adrenals were slightly desiccated; the pancreas was very firm, dry, and appeared normal; the œsophagus was contracted and very hard.

The stomach was tightly contracted, firm; its mucous membrane well preserved and thrown into prominent rugæ. It contained a little semifluid matter of the color of coffee-grounds. The peritoneum was shiny, very dry, and light-colored, like paper. An abnormal band constricted the ascending colon about its middle, and the cæcum appeared considerably dilated.

The colon contained considerable brownish desiccated fecal matter. The muscular system was very dry, tough, and of a bright-red color. The aorta and large arteries were very tough, dry, and shrunken; the large veins were firm and contained a little clotted blood; in some places they were decolorized and gelatinous.

On *microscopical examination*, the wall of the pharyngeal (abscess) cavity was found to be composed of intensely inflamed granulation-tissue in the older portion and of connective and muscular tissue infiltrated with serum; blood and leucocytes were found in the deeper portion. A section of the wall of the carotid just above the point of rupture showed this vessel running through an area of advanced purulent inflammation. At this point the adventitia was œdematous, the muscular coat split up, and at one point very thin. The intima appeared intact. In the same section the wall of the internal jugular vein was so infiltrated with leucocytes and serum that its structure was almost indistinguishable.

The cervical lymph-nodes showed an intense exudative inflammation, but no collections of pus were seen. They showed considerable post-mortem necrosis. The consolidated lobules of the lungs were filled with a homogeneous reddish substance, without signs of inflammation either in the parenchyma or bronchi.

The cells of the liver were partly necrotic; the cell-bodies, stained faintly, were extensively vacuolated and coarsely granular; the cell-membranes were very distinct and the nuclei faint. Many capillaries were stuffed with leucocytes, which sometimes appeared in collections of 50 to 100, both mononuclear and polynuclear.

The cells of the kidneys showed usually partial granular fragmentation, but many appeared entirely intact and normal. There were no evidences of an inflammatory process. In the spleen there was considerable increase of mononuclear and polynuclear cells, both in the pulp and in the Malpighian bodies. All the structures were well preserved. The stomach-wall was normal, with very little superficial post-mortem necrosis of the epithelial lining.

Sections through the wall of the cavity stained by methylene-blue showed numerous colonies of cocci. No bacilli or chain-cocci could be distinguished.

The anatomical diagnosis was peritonsillar and retro-pharyngeal abscess;

inflammation and rupture of the right internal carotid artery; healed croupous inflammation of the tonsils; purulent inflammation of the large branch of the internal jugular vein.

EPICRISIS. The history and pathological examination indicate positively the development of a peritonsillar and retropharyngeal abscess following a croupous tonsillitis. As no Klebs-Loeffler bacilli were found in the bacteriological examination of the Health Board, the croupous inflammation was of staphylococcous origin, in accordance with the above results of the bacteriological examination. The first hemorrhages must have resulted from rupture, following inflammation of veins or arteries attacked by the advancing suppuration. The fatal hemorrhage undoubtedly came through the openings demonstrated in the internal carotid artery and pharyngeal wall, a necessarily fatal lesion. The condition of the internal jugular vein indicates that it or its branches were possibly the point of origin of the first hemorrhage. The second hemorrhage, which is reported to have been very copious and of bright color, must have been arterial.

Is it possible to make a correct diagnosis of the source of such a hemorrhage? Many a case may be decided by the character of the blood, whether arterial or venous; but in many septic conditions the color of the arterial blood is no longer bright, and from a large septic cavity the discharge may be both arterial and venous. In exceptional cases (as was remarked by Guthrie fifty years ago, and by Lidell, Roux, Wahl, and others) a large lacerated artery with a ragged interior or irregular edges may, while bleeding, exhibit a murmur. In other cases, when the question is between a hemorrhage from the carotid and the nasopharynx, the digital compression of the artery is, in an urgent case, provided a medical man is present, more likely to answer the inquiry as to the source of the bleeding.

During the progress of an inflammatory and suppurative process round cells are caused to proliferate near the vasa vasorum of the media, and the endothelia of the intima multiply rapidly. In this way the resistance of the vascular tube is increased, and many a threatened calamity may thus be avoided. When, however, a rupture of the bloodvessel-wall has taken place the hemorrhage depends on the size of the laceration and also on the condition of the patient. For every hemorrhage creates a disposition to its cessation by lowering of the blood-pressure; there may even be syncope, and a clot

may form. But within a single day, or several days, the amount of circulating blood is increased, the heart becomes more vigorous, and the clot is expelled. In cases of ulcerous erosion, when the patient has suffered from a septic process, circumstances are least favorable. In them there are rarely long intervals between the hemorrhages. Fatal cases of that nature are not very common. A certain number have been observed in syphilis, sometimes in the course of an arteritis, mainly in the young, in whom the skin, the brain, or the periosteum is frequently subject to bleeding from that cause. Metrorrhagia has been observed under the same circumstances (Bradley). Gummata located in the bloodvessel-walls, or more often in their neighborhood, will ulcerate and lacerate. Thus, Bernhard (*Lancet*, 1872) had to ligate the common carotid because of formidable hemorrhages originating in the larynx. Morell Mackenzie[1] cites the case of a hemorrhage probably from a vertebral artery, as the patient expectorated the transverse process of his epistropheus. Landrieux[2] describes the case of a patient who had gummas in very many organs, besides periostitis. His pharynx was full of ulcerations and cicatrices; one of the ulcerations communicated with the internal carotid. He died of the second hemorrhage, which took place two days after the first.

Parenchymatous or venous bleeding, more or less copious, sometimes fatal (as in the case of Rosenthal's), in scarlatina, diphtheria, and hæmophilia, or in septic processes complicated with leucocythemia or scurvy, have been seen frequently. Trifling extravasations from dilated bloodvessels behind the uvula or in the nasopharynx, which now and then are mistaken for hæmoptysis, I do not here count. In a single case I saw also a fatal series of hemorrhages in an old man who had inaccessible sclerotic veins in his posterior nares.

What concerns us here is a fatal hemorrhage from erosion of an artery complicated with phlebothrombosis. The lesion of the artery was evidently the result of local suppuration. Eighty-eight such cases of hemorrhage from large arteries caused by suppuration were collected by Monod. In thirty-seven they were occasioned by abscesses in the soft parts—viz., tonsil, retropharynx, lymph-bodies of the neck, and secondary processes in typhoid fever and in scarlatina. In many cases the internal carotid, in two the aorta, were injured.

[1] Diseases of the Throat and Nose.

[2] Bull. Soc. Anat., Paris, July, 1874.

Monod had also two cases of inguinal buboes with erosion of the femoral artery; Koenig, who in 1889 quoted Monod, suggested that many of these hemorrhages were caused by *pus bonum et laudabile;* in 1898 he would not make this distinction, at least not with the same assurance. For there may be undoubtedly a destructive effect as well of an uncomplicated staphylococcous process as of a mixed infection.

Fatal cases of erosion of large bloodvessels in the throats of septic children are, however, not very frequent. I knew of no case when I published my *Treatise on Diphtheria* in 1880. V. Gautier, it is true, had two fatal cases of pharyngeal hemorrhage—one quoted from Rendu, who found the carotid and its branches intact, and one of his own, in which vertebral caries was found, but the source of the hemorrhage was not discovered.[1] Greenhow[2] quotes Williams, who had a fatal case, in which the patient died apparently from the profuse discharge of bloody material, resembling claret, from the throat, amounting to two pints a day; but here, too, the local lesion was not found. Still Becquerel[3] had previously published a case of death resulting from an ulcerous lesion of the inferior pharyngeal artery. Quoting this case, Greenhow adds: "Probably some of the cases of fatal hemorrhage on record in this country (England) have really arisen from gangrenous ulceration." Carmichael[4] related the case of a baby of five weeks, who had a feverish cervical adenitis. Respiration and deglutition became worse in two days, and the patient died in a hemorrhage. The retropharyngeal abscess communicated with the post-tonsillar cavity; the open artery was the external carotid.

In the *Medical News* of February 19, 1898, there is the report, by Franklin, of the case of a child seven years old. There were retropharyngeal abscess, collapse, hemorrhage from mouth and nose, probably from the neighborhood of the left tonsil; on the following day aphasia, hemiplegia and anæsthesia of the right side. Slow recovery took place, with the exception of partial paralysis of the right arm, and talipes equino-varus. Presumably, the abscess broke into the left carotid artery.

Bokay and Alexey[5] have recorded the case of a boy of four years,

[1] Des abscès retrophar. ou de l'angine phlegmoneuse. Bâle, 1869.
[2] Diphtheria, 1860, p. 209.
[3] Gaz. Méd. de Paris, 1843, p. 692.
[4] Edin. Med. Journ., July, 1881.
[5] Jahrb. f. Kinderheilk., 1881, xvii. p. 209.

who had an inflamed throat three weeks. No diagnosis was made. Then his fever rose to 40° C., his face became œdematous, his throat red, but no local abscess or swelling was discovered. There being dyspnœa, the case was considered one of probable pneumonia. Besides he had a nephritis, probably scarlatinous. One night there was a hemorrhage of 350 c.cm., and the next morning another. The autopsy was made by Szekeres, under whose name this case appears in some of the records, so that it has often been counted twice. There was pus in a tonsil and in the surrounding tissue, and in a cavity of the size of a hazel-nut was the perforation of a common carotid.

The new, elaborate, and exact *Traité des Maladies des Enfants*[1] has only this to say on the subject, that gangrene will sometimes advance into large bloodvessels.

[1] In five volumes, by Grancher, Comby & Marfan (i. p. 555).

THE EFFECT OF FREEZING UPON THE ANTIDIPHTHERIA SERUM.

By HAROLD C. ERNST, A.M., M.D.,
PROFESSOR OF BACTERIOLOGY IN HARVARD UNIVERSITY.

My attention was attracted a short time ago by an indefinite reference to Buchner's work upon the effect of freezing upon the germicidal properties of the blood, the reference to which I have been unable to verify. The thought occurred to me that if freezing had any effect in throwing down these germicidal properties from one layer to a lower one, the result might be obtained by putting antitoxic serum through the same process; and, further, that this might, if successful, be of some practical interest.

What I have to report is the result of some tests made in this direction with the serum of several horses that were being used for the production of diphtheria antitoxin under my care. The plant of which I have had charge has been given up, and, therefore, the facility with which I have been able to secure sufficient quantities of serum for such experiments has been done away with; but it seemed well to report the results so far as they have been carried out. The work has been done under my general direction by Drs. J. N. Coolidge and H. A. Cooke.

The method was as follows: Test-tubes full of serum of a definite strength were frozen for a day, allowed to melt, refrozen, again allowed to melt, and so on for a number of days in succession. At the end of the time determined upon—usually about a week, and sometimes longer—the frozen column of serum was cut while solid to secure a more or less exact division, melted, and its unit strength again determined.

Dr. Cooke has given certain details in regard to the cutting of the frozen serum in the test-tubes which may be of interest to any one who may wish to try this method:

The tube is dipped in scalding water for a few seconds to loosen the stick of "serum-ice" from the sides. When loose enough to turn slightly in the tube, the bottom of the tube is cracked with a sharp blow so as to admit air and permit the stick to slide from the mouth. It is caught upon a sterilized towel, which has generally been spread upon a basin of cracked ice, to prevent the stick from melting before it could be cut. The cutting is done with a knife that has been kept in boiling water for a few minutes, and the stick is cut into four parts of as nearly equal size as can be estimated by the eye.

After the lower layer of syrupy serum has been well separated out from the rest it freezes with some difficulty, and when frozen melts so readily that it is often difficult to preserve it all in the cutting. Sometimes also a temperature low enough to freeze the upper three-quarters of the tubeful of serum will not affect the lower quarter. In such cases I have cracked a piece out of the bottom of the tube and poured out this syrupy serum before slipping the frozen portion out of the other end. The distinct coloration generally extends slightly up into layer No. 3, except where a small-calibered test-tube has been used and has been filled nearly full with serum. For an ordinary sized test-tube filled about three-quarters full, a division of the frozen serum by thirds would be more rational if color be taken as the basis of division into layers. Where it is divided into quarters the upper portion of layer 3 is practically colorless. There appears to be a difference, however, in different serums in this respect. In some the lowest quarter contained nearly all the color, and was of so syrupy a consistency as to pour with difficulty. In one or two instances the serum at the very bottom of the tube was gummy and would not pour at all.

After cutting the serum-ice the pieces are put into sterilized Petri dishes, allowed to melt, and then bottled. In layer No. 1 (top layer), after melting I have frequently noticed small, extremely thin, nearly transparent crystalline plates floating about; I have not investigated these. Similar ones have not been noticed in any of the other layers. They apparently persist, for they have been recently seen in some of the top layers put up in the beginning of the series of tests.

The top layer often contains merely the faintest trace of albumin; the chemical analysis of these layers and a comparison of their composition with the ordinary serum of the horse is a matter for future investigation.

The changes in the appearance of the serum were very marked, and became apparent after the second freezing, sometimes slightly so after the first. The upper portion lost all color and became, to all appearances, water, while the lower part became darker in color and much less fluid, this being so marked that often the bottom layers would not flow from the test-tube, adhering to the sides as a sticky

1 day.

4 days

8 days.

mass of a more or less deep red color, the latter depending upon the amount of hæmoglobin present in the original serum.

The sections into which the frozen serum was cut were numbered 1 to 4, from the top downward, in our own experiments, and, without giving details, this brief summary of them will serve to show the results:

Serum from six horses was tested as follows: Serum of 40 units (of which 1 : 400 c.c. protected against ten times the fatal dose of toxin); frozen on twelve successive days. The top layer was found to have practically no protective power, while the bottom layer was of an approximate strength of 100 units to the c.c. (less than 1 : 800 and more than 1 : 1200 c.c. protected against ten times the fatal dose of toxin).

Serum of 100 units (of which 1 : 1000 c.c. protected against ten times the fatal dose of toxin); frozen seven successive days. The top layer was found to have practically no protective power, whilst the bottom layer was of approximately 300 unit strength (less than 1 : 2000 and more than 1 : 5000 c.c. necessary to protect against ten times the fatal dose of toxin).

Serum of 60 units (of which 1 : 600 c.c. protects against ten times the fatal dose of toxin); frozen twelve days and melted each day; another portion was frozen twenty days under the same conditions. The top layer was found to possess practically no protective power; the bottom layer was of about 180 unit strength (very slightly less than 1 : 1800 c.c. protects against ten times the fatal dose of toxin).

Serum of 40 units strength (1 : 400 c.c. protects against ten times the fatal dose of toxin); frozen eight days, as the others. Approximately of 100 unit strength in the bottom layer (less than 1 : 800 and more than 1 : 1200 c.c. protects against ten times the fatal dose of toxin; the top layer has apparently no protective power).

Serum of 30 units strength (1 : 300 c.c. protects against ten times the fatal dose of toxin); frozen eight days. The top layer has no protective value; the bottom layer of 100 unit strength (1 : 1000 c.c. protects against ten times the fatal dose of toxin).

Serum of 100 units strength; frozen eight days and melted each day, like the others. Approximately of 300 unit strength. The top layer has practically no protective power; the bottom layer protects in a dose of almost 1 : 3000 c.c. against ten times the fatal dose of toxin.

Dr. W. H. Park, of New York, was good enough to send us some of the serum produced under his control. This was frozen by us, divided, and returned to him for testing, without his knowing what had been done to it. Two lots were sent back to him from the amount which he sent to us.

Lot 1. Frozen eight days. Original strength 300 units to the c.c.

Dr. Park reports No. 1 (bottom layer) is about 400 units to each c c. (400 to 450); No. 2 (layer next to the bottom) is about 300 units to each c.c. (300 to 320); No. 3 (layer next to top) is under 300 units to each c.c.; No. 4 (top layer) is under 300 units to each c.c.

Lot 2. Frozen twenty days. Original strength 300 units to the c.c.

"The first series shows No. 4 (bottom layer) to have over 600 units full, as pigs getting ten times the fatal dose with 1 : 5000 and 1 : 6000 c.c. lived; No. 3 (layer next the bottom) was under 160 units; No. 2 (layer next the top) under 80 units, and No. 1 (top layer) under 40 units."

No. 1 (bottom layer) of the first lot is over 500 units per c.c.

Dr. Theobald Smith, of Boston, was also good enough to submit some of the serum produced under his control to our experiments, and to test the product after it was returned. It is to be noted that in this case the freezing and separation of the serum were not carried so far as in our own or in that of Dr. Park. It was frozen six days, separated, and returned to Dr. Smith. His report is as follows:

"The following statement gives the essence of the test to determine the neutralization power of the fluids furnished me:

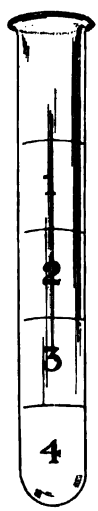
	Guinea-pigs.	
	110 units.	130 units.
Control serum ix, 17. plus 10 t. f. d. toxin .	No effect.	Dies in $1\frac{3}{4}$ d.
Fluid No. 1 " " " .	"	No effect.
" No. 2 " " " .	"	Dies in $2\frac{1}{6}$ d.
" No. 3 " " " .	"	" $1\frac{1}{2}$ d.
" No. 4 " " " .	Dies in 1 d.	" 1 d.

"This test shows that the serum furnished (or a bottle of the same drawing) was 110 units strong; that No. 1 (bottom layer) increased, apparently or actually, the strength to 130 or above; that No. 2 (next to the bottom layer) showed a slight increase over the control serum; that No. 3 (next to the top) was weaker than the control; that No. 4 (top layer) was very weak—actual strength not determined. The

upper neutralization limit of No. 1, the lower limit of No 4 (water?), and the exact strength of Nos. 2 and 3 can only be gauged accurately in a supplementary experiment requiring many animals."

I desire, of course, to acknowledge the obligation I am under to these gentlemen for the trouble to which they have put themselves in carrying out these tests for me. The results seem to show very definitely that the antitoxic property can be removed from one portion of the serum and added to another by the method of what may be called "fractional" freezing. The practical value of the method—which may be extended to extremes of slenderness of the column of serum and number of freezings—in obtaining serum of high potency that is more or less permanent, and this without the dangers to the animals under ordinary methods of forcing the dosage of toxin, is, of course, evident. Another possibility is that the exact nature of the antitoxic property may by this means be made out.

The result of the first series of experiments as represented in the table shows very graphically the changes in the power of different layers of the serum after freezing:



	1st day.	2d day.	3d day.	Six weeks after.
1/800	Losing	Dead		
1/400	Losing	Dead		
1/800	Losing	Dead		
1/400	Losing	Losing	Dead	
1/800	Losing	Losing	Dead	
1/400	Losing	Gaining	Gaining	Well
1/800	Losing	Gaining	Gaining	Well
1/400	Losing	Gaining	Gaining	Well

The table represents the gradual increase in protective power in the lower layers of a test-tube of serum that has been frozen for a number of successive days—one eight-hundredth and one-four-hun-

dredth of a c.c. from each division of the serum injected against ten times the fatal dose of toxin. No protective value in the upper half of the tube.

(NOTE.—Curiously enough, the article of Bujwid (*Cent. f. Bakt.*, Erste Abt., 1897, p. 287) upon the same subject had entirely escaped our attention until this work was done.)

ON NEPHRITIS OF MALARIAL ORIGIN.

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THE fact that albuminuria may occur in the course of malarial fever as well as during other acute infections is well known. Martin-Solon[1] estimated that it was to be found in a quarter of all cases. Laveran,[2] however, believes that this is a high percentage for the simple non-pernicious fevers. Joseph Jones[3] refers to its occasional occurrence, but says: "In several hundred examinations of the urine of the different forms of malarial fever in the Marine Hospital at Savannah, Georgia, albumin was found in only one case, which was complicated with typhoid fever. This fact is important in its bearing upon typhoid and yellow fever." Anders,[4] in 1780 cases collected from the records of various hospitals in Philadelphia, noted only eighteen instances in which albuminuria ("marked") was found. Hertz[5] asserts that "it is no very uncommon thing to find albumin present in considerable quantities." . . . "Albumin is to be found in the urine either only on the fever days or during the intermission as well (fibrinous tube-casts have also been observed), and disappears on recovery." Atkinson[6] studied the urine in seventy-six cases of intermittent and remittent fever, in which albuminuria occurred five times; in a second series, however, occurring during the late summer and fall of 1883, forty-five in number, albuminuria was noted in six instances. Kelsch and Kiéner[7] assert that in ordinary malarial fevers "the presence of albumin is not rare in paroxysms of a certain intensity, but it is particularly common in relapses in old sufferers, where the kidney is

[1] Gaz. Méd. de Paris, 1848, iii. s., t. iii. Année, xix. 618.
[2] Traité du Paludisme, 1898, 8°, Paris.
[3] Medical and Surgical Memoirs, vol. ii. p. 772.
[4] Journal of the Amer. Med. Asso., 1895, vol. xxiv. p. 916.
[5] Ziemssen's Cyclopædia, American edition, vol. ii. p. 641.
[6] Amer. Journ. Med. Sciences, 1884, vol. lxxxviii. p. 149.
[7] Maladies des pays chauds, p. 144.

already altered." They say that in the more severe bilious and gastric fevers (page 453) "albumin is frequent enough but inconsiderable and transient; it may be intermittent and disappear with the paroxysm, or it may continue during the intermission."

Despite the relative frequency with which some observers have noted albumin in the urine of malarial patients, its presence or absence has been used as a point in the differential diagnosis between certain forms of severe malaria and yellow fever, in which latter affection the early appearance of albumin is the rule. McLean, in *Reynolds' System of Medicine*, says: "Albuminous urine is almost invariable in yellow fever—only occasional in remittent." Again, of the urine in remittent fever, he says: "It seldom contains albumin . . . albuminous urine is the rule in yellow fever, a rare exception in remittent."

Ascoli,[1] Dubujadoux,[2] and others have noted the existence of peptonuria in association with the malarial paroxysm.

The occurrence of acute nephritis in connection with malaria has also been recognized for many years: Chénouard,[3] Hertz,[4] Soldatov,[5] Dewalsche,[6] Verhaeghe,[7] Schmid,[8] Pepper,[9] Busey,[10] McLean,[11] Da Costa,[12] Wood,[13] Rosenheim,[14] Atkinson,[15] Bermann,[16] Stefanowicz,[17] Dods,[18] and many others noting this condition.

Throughout the Southern States, as testified to particularly by the admirable records of Joseph Jones,[19] the condition is not very infrequent. The grave and often fatal acute nephritis following hæmoglobinuric attacks is well known. These cases have been well studied by Bastinelli[20] and Kelsch and Kiéner,[21] who have described at length the changes in the kidneys following acute malaria. They believe that severe acute, diffuse, or glomerulo-nephritides may directly

[1] Lav. d. Cong d. Med. Int., 1892, Milano, 1893, vol. v. p 350.
[2] Arch. de Méd. et Pharm., Paris, 1892, p. 437.
[3] Rec. des travaux de la Soc. Méd. du Depart. d'Indre-et-Loire, 2s, 1845, p. 101.
[4] Op. cit.
[5] St. Pet. Med. Woch., 1878, iii. 345.
[6] Arch. Belges de Méd. Mil., 1859, xxiii. 20.
[7] Ibid., 1860, xxvi. 31.
[8] Deutsche Klinik, 1852, 442.
[9] Amer. Journ. Med. Sci., 1866, li. 405, 408.
[10] Ibid., 1873, lxv. 123.
[11] Op. cit.
[12] Med. Record, N. Y., 1880, xvii. 54.
[13] Ibid., 1888, xxxiii. 320.
[14] Deutsch. med. Woch., 1886, xii. 752.
[15] Op. cit.
[16] Internat. klin. Rundschau, Wien, 1894, viii. 1844.
[17] Wien klin. Woch., 1893, vi. 365.
[18] Edinb. Med. Journ., 1888, xxxiii. ii. 1890.
[19] Op. cit.
[20] Ann. di Med. Navale, Anno ii. 1896.
[21] "Maladies des pays chauds," 8vo, Paris, 1889, and Arch. de Phys. norm. et path., Paris, 1882, 2 s., ix. 278, 458.

depend upon the malarial infection. They assert that nephritis occurs in more than half the fatal cases. "It develops in cases where the disease has a relatively long duration and has been marked by symptoms of corpuscular dissolution, especially by hæmoglobinuria, from which we may conclude that it depends less upon the direct action of the malarial poison on the kidney than upon the irritation produced in the gland by the passage of the hæmoglobin and its derivatives."

Bignami,[1] in his valuable studies upon the anatomical alterations in acute malarial infections, noted the fact that the kidneys were, as a rule, but little affected. The glomeruli were markedly pigmented, the pigment granules sometimes being within large colorless cells, sometimes apparently within the endothelium of the glomerulus; at times, the most important lesions consisted of an exfoliation and degeneration of the epithelium lining the capsule; only in algid pernicious fever did he find glomeruli with very slight albuminous exudates. Sometimes, however, marked and extensive alterations of the parenchyma were found, consisting of focal necrosis of the epithelium, especially those of the tubuli contorti.

Barker,[2] in four fatal cases of malaria, found in three instances that the kidneys showed but few changes, consisting of a slight pigmentation of the glomeruli with albuminous exudates and casts, and a more or less swollen and degenerated condition of the epithelium of the convoluted tubules. A fourth instance was one of marked acute nephritis which was probably of malarial origin, although complicated later in its course by a streptococcus infection—Case II. of our series. In Anders'[3] 1780 cases there were but four instances of acute nephritis.

The frequency of the occurrence of *chronic nephritis* as a result of malarial fever is a point about which different opinions have been held. Lenz[4] and Rosenstein[5] both believed malaria to be a frequent cause of chronic nephritis. Bartels[6] was also a strong upholder of this idea. Herz[7] likewise asserts that cases of acute nephritis in malaria may pass into a chronic diffuse process, a sequence which is recognized by many

[1] Atti della R. acc. med. di Roma, 1890, Anno xvi., s. ii., v. 317.
[2] Johns Hopkins Hospital Reports, 1895, v. 230.
[3] Op. cit.
[4] De diffusa nephritide chronica, præcipue respecto decursu morbi post intermittentem febrim, 8°, Gryphiæ, 1865.
[5] Path. u. Therap. der Nierenkrankheiten, Berlin, 1870, 215.
[6] Ziemssen's Cyclopædia, Amer. edition, vol. xiv. p. 328.
[7] Op. cit., p. 649.

observers. McLean[1] says: "I can confirm from personal observations Dr. Parke's remark that chronic Bright's disease is a consequence of ague. Many 'old Indians' who have suffered from malarial fevers die of this disease."

Kelsch and Kiéner[2] have described in detail the changes in chronic as well as in acute nephritis occurring in cases of old "fébricitants." They describe two main varieties of kidney as met with in chronic paludism: (1) the congested kidney; (2) the atrophic kidney.

1. The engorged kidneys are increased in size and weight and of firm consistency. The surface is smooth, the color deep red, the congestion being particularly marked in the pyramids. Owing to the extensive congestion of the vessels, interstitial hemorrhages or the escape of blood into the tubules may occur. There is a marked granular degeneration of the tubular epithelium, while desquamation is common. Hyaline casts may be found.

2. The atrophic kidneys are small, the surface is irregular, the capsule adherent, the consistency increased. The color is usually of a maroon or mahogany tinge, and often there is a blotchy appearance. Small cysts are common. Microscopically, alterations are to be found in the interstitial tissue as well as in the tubular epithelium. They note in conclusion[3] that "malarial nephritides have but little that is characteristic about them. We may again, however, note: (1) The tendency toward hemorrhages in all forms and at all periods of the nephritis. (2) The frank character of the inflammation in contradistinction to the partly steatotic, partly sclerotic forms which gout and alcoholism give rise to so frequently with us. (3) The rarity, perhaps the absence of amyloid degeneration, the ordinary expression of septicæmia of all sorts. Even in the cachexias the fatty and colloid degenerations of the kidneys are of a subinflammatory character and give rise to hemorrhages. They are sharply distinguishable from the lesions of the senile kidney by the wholly secondary importance of the vascular changes, and notably by the absence of arterial atheroma."

Rowland[4] noted the frequency of chronic nephritis in the malarial

[1] Reynolds' System of Medicine, vol. i.

[2] Maladies des pays chauds, 8vo, Paris, 1889, 744; Arch. de Phys. norm. et path., 1882, s. 2, t. ix. p. 278.

[3] Arch. de Phys. norm. et path., 1882, s. 2. t. ix. 494.

[4] The British Guiana Medical Annual and Hospital Reports, Demerara, 1892, 41.

regions of British Guiana. Laveran,[1] in his treatise, states that "acute or chronic nephritis is a fairly common complication of paludism. The nephritis has sometimes the characters of an epithelial nephritis (the urine contains albumin in great quantity, anasarca occurs and becomes rapidly generalized), sometimes those of interstitial nephritis or of mixed nephritis; this last form is, I believe, the commonest."

Other observers have paid very little attention to malaria as a cause of chronic renal changes. Thus, it is not mentioned in Senator's[2] work as an etiological factor in chronic nephritis. Anders,[3] in 1780 cases of malaria, met with chronic nephritis in but one instance. Bignami,[4] in his admirable studies on the pathological anatomy of chronic malarial infections, lays but little stress on the changes in the kidneys.

Marchiafava and Bignami[5] have described amyloid degeneration of the kidneys following long and repeated febrile attacks. These cases had been associated with clinical and anatomical manifestations of a severe chronic nephritis. Beside the affection of the vessels of small and medium size and of the glomeruli, the authors found a considerable involvement of the walls of the renal tubules themselves.

Rem Picci,[6] of Rome, has recently published an interesting communication upon the renal lesions in malarial fever, which has come to the author's observation since the writing of this paper. He recognizes the fact that a malarial infection may be the cause not only of simple albuminuria, but of extensive renal changes, although such cases are rare. Malarial nephritis occurs more commonly in the fall than in the spring, and is particularly common in young individuals. It occurs in both the severe and the mild forms of the disease, and is no more frequent, apparently, in the former than in the latter.

The attack is usually mild and of favorable outcome, but it may be severe, and in some instances passes into a chronic form. The symptoms of nephritis appear not only during the malarial attack, but sometimes develop after the disappearance of the symptoms of the

[1] Op. cit., p. 213.

[2] Die Erkrankungen der Nieren, Wien, 8vo, 1896. (Excerpt from Spec. Path. u. Therap., herausgegeben v. Nothnagel.)

[3] Op. cit.

[4] Boll. d. R. acc. Med. d. Roma, 1893, xix. 186.

[5] Riforma Medica, 1891, Anno vii., vol. i. 571.

[6] Il Policlinico, vol. v-M., 1898, 197.

infection. These cases Rem Picci has termed "post-malarial." Amyloid degeneration is occasionally met with. The exciting cause of malarial nephritis is believed by the author to be the irritation of the kidney due to the elimination of the toxic products of the infection.

Thus, in summary, it may be seen that the association of albuminuria with malarial fever has been generally recognized, but its frequency variously estimated, the general tendency being toward the idea that, even in severe forms, it is not so common but that the early appearance of albuminuria may be regarded as a valuable point in the differential diagnosis between this disease and yellow fever. And while acute nephritis dependent upon malarial infection is well understood to occur, there are no existing statistics tending to show its relative frequency as compared with nephritis in other acute infections. The same may be said with regard to the more chronic renal changes. It has therefore seemed advisable to us to analyze our cases of malarial fever occurring during the last eight years, with a view to determining the following points:

1. The frequency of albuminuria in malarial fever as compared with other acute infections.
2. The frequency of acute nephritis in malarial fever.
3. The possible influence of malarial fever in the production of chronic renal changes.

ALBUMINURIA.

During the past eight years 758 cases of malarial fever have been treated in the wards of the Johns Hopkins Hospital. In 691 of these cases there are records of examination of the urine.

Albumin was present in 321 instances—46.4 per cent.

There was no albumin in 370 instances—53.5 per cent.

In the great majority of cases the albumin was present as a small trace.

Casts of the urinary tubules were found in 121 cases—17.5 per cent.

The proportion of cases in which albuminuria was present varied materially, as might have been expected, according to the type of fever.

TABLE OF 691 CASES IN WHICH AN EXAMINATION OF THE URINE WAS RECORDED.

Tertian fever—344 cases:				
Albumin present in	132	cases.—	38.3	per cent.
No albumin "	212	"	61.6	"
Casts "	40	"	11.6	"
Quartan fever—8 cases:				
Albumin present in	4	cases.—	50.0	per cent.
No albumin "	4	"	50.0	"
Casts "	3	"	37.5	"
Regularly intermittent fevers (tertian and quartan)—352 cases:				
Albumin present in	136	cases.—	38.6	per cent.
No albumin "	216	"	61.3	"
Casts "	43	"	12.2	"
Æstivo-autumnal fever—283 cases:				
Albumin present in	165	cases.—	58.3	per cent.
No albumin "	118	"	41.6	"
Casts "	70	"	24.7	"
Combined infection (tertian and æstivo-autumnal)—26 cases:				
Albumin present in	11	cases.—	42.3	per cent.
No albumin "	15	"	57.6	"
Casts "	7	"	26.9	"
Cases of uncertain type—30 cases:				
Albumin present in	9	cases.—	30.0	per cent.
No albumin "	21	"	70.0	"
Casts "	1	"	3.3	"

It thus becomes evident that albuminuria has occurred in nearly one-half of all the cases of malarial fever treated in the hospital. In the regularly intermittent fevers, tertian and quartan, the proportion of cases of albuminuria was 38.6 per cent., while in the æstivo-autumnal infections, the majority of all cases, 58.3 per cent., showed albumin in the urine. The large percentage in æstivo-autumnal fever is not remarkable when one considers the many other clinical evidences of the greater malignancy of infections with the æstivo-autumnal parasite.

Our statistics show, however, a rather strikingly large proportion of instances of albuminuria in all types. They can scarcely be compared to those of Anders, who has used the qualifying term "marked."

The percentage is, however, five times as large as that of Atkinson,[1] who found albuminuria in 9 per cent. of 121 cases.

Particularly conspicuous is the high percentage of albuminuria among the cases of æstivo-autumnal fever. It is in the more severe infections with this variety of parasites that the so-called remittent and pernicious fevers most commonly occur, and in these more severe attacks it would be but fair to assume that the percentage of cases showing albumin would be yet larger than that shown by our figures. And yet it is in just these cases that, at times, the question of a differential diagnosis between yellow fever and malarial fever is believed by some authors to hang upon the presence or absence of albumin in the urine.

It may be interesting to compare the frequency with which we have found albumin in the urine of patients with malarial fever with our own statistics and those of others with relation to certain other of the acute infectious diseases.

Typhoid Fever. Here we may use our own statistics. In 389 cases of typhoid fever from the statistics of Hewetson and Osler, albumin was observed in 303 instances, or 78 per cent., and casts in 164, or 42.2 per cent.[2]

Scarlet Fever. The frequency of albuminuria in scarlet fever has been variously estimated. Miller,[3] Patrick,[4] Steiner,[5] and Guebler,[6] as well as Lecorché and Talamon,[7] believe that albuminuria is practically always present during the febrile period of the disease. Sée[8] estimated that it was present in more than one-half the cases; Haidenheim in 80 per cent.[9] Cadet de Gassicourt[10] found albumin in 21 out of 65 cases, but believes these figures to be too high. Barthez and Sanné[11] believe it to be relatively rare, while Vogel[12] found it in two instances out of 50 or 60 cases, and Thompson[13] in 40 out of 112 instances.

[1] Op. cit.

[2] Hewetson: Johns Hopkins Hospital Reports, 1894, iv. 113. Osler: Johns Hopkins Hospital Reports, 1895, v. 281.

[3] Lancet, 1849, ii. 1, 57, 113, 197, 281, 524, 685.

[4] Cited by Guinon: Art. "Scarlatine," in Traité de Méd., Charcot, Bouchard, Brissaud, 8vo, Paris, 1892, t. ii.

[5] Compendium der Kinderkrankheiten, 3d ed., 8vo, Leipsic, 1878.

[6] Dict. Encycl. des Sci. Méd., Par., 1869, ii. 476.

[7] Cited by Guinon: Op. cit.

[8] Le Moniteur des Hôp., 1858, 659.

[9] Cited by Barthez and Sanné.

[10] France Méd., Par., 1881, ii. 388, 400.

[11] Traité clin. et prat. des maladies des enfants. 3d ed., Par., 1891, 124.

[12] Cited by Barthez and Sanné.

[13] Med.-Chir. Transactions, 1887.

The later albuminuria, that occurring during convalescence, was observed in 30 per cent. of the cases of Cadet de Gassicourt, and in 55 out of the 112 cases studied by Thompson.

Caiger,[1] in the London Fever Hospital, found albuminuria present in but 7.69 per cent. of 4015 cases; he asserts that the frequency of this condition is much less than is generally supposed. He omits, however, from his statistics those cases in which "but a faint and transient cloud of albumin was noted for less than three days."

My friend, Dr. McCollom, has very kindly sent me the results of the examination of the urine in 100 cases of scarlet fever in the Boston City Hospital:

¼ to ⅛ per cent. of albumin	4 cases.
$\frac{1}{10}$ per cent. of albumin	1 case.
Large trace " "	1 "
Trace " "	4 cases.
Slight trace " "	14 "
Very slight trace of albumin	15 "
Slightest possible trace of albumin	49 "
No albumin	12 "
	100 cases.

Diphtheria. The frequency of albuminuria in diphtheria is also variously estimated. Sée[2] believed it was present in one-third or a half of all cases. Maugin and Bergeron[3] assert that it occurs in the majority of instances. Bouchut and Empis[4] estimate its frequency at 66⅔ per cent., as does also Ebert.[5] Smith[6] found it present in 24 out of 62 cases, or 38.7 per cent., but believes that the proportion is probably greater, inasmuch as albumin was often missed, owing to the transient character of the symptoms. Sanné[7] found albumin in 224 out of 400 cases, or 54.5 per cent. By far the most satisfactory statistics are those of McCollom.[8] Out of 623 cases of diphtheria albumin was present in 57.7 per cent.

If we compare our statistics of malarial fever with those of *typhoid*

[1] Article "Scarlet Fever," in "A System of Medicine," etc., edited by T. Clifford Allbutt. London, 1897, vol. ii. 151.

[2] Op. cit.

[3] Moniteur des Hôpitaux, Par., 1858, vi. 1035, 1043, 1051, 1064.

[4] Gaz. des Hôp., 1858, 524.

[5] Cited by Oertel, Ziemssen's Cyclopædia, Amer. edition, i. 603.

[6] Keating's Cyclopædia of Diseases of Children, i. 626.

[7] Traité de la diphthérie, 8°, Par., 1877, pp. 128 et seq.

[8] Med. and Surg. Reports, Boston City Hospital, 9th series, Boston, 1898, p. 27.

fever we find that malaria stands well behind the former affection in the frequency with which albuminuria is observed. The figures show:

Percentage of cases of albuminuria in malarial fever	46.4
" " " typhoid fever	78
" " in which tube casts were found in malarial fever .	17.5
" " " " " typhoid fever .	42.2

This is not remarkable when one considers through how long a period the kidneys of a patient with typhoid fever are subjected to the influence of the toxic products of the infection, as well as to the continued high temperature.

If, however, we compare the percentages in the more severe æstivo-autumnal fevers, the figures approach one another more closely:

Percentage of cases of albuminuria in æstivo autumnal fever . .	58.3
" " " typhoid fever	78
" " in which casts were found in æstivo-autumnal fever	24.7
" " " " " typhoid fever . .	42.2

Scarlet Fever. From a consideration of the varying estimates above mentioned it would appear that albumin is in all probability present in at least one-half the cases of scarlet fever. McCollom's figures indicate a still higher percentage. It is, perhaps, possible that in a certain proportion of the 49 per cent. of cases where the "slightest possible trace of albumin" was found this minute quantity would have passed unobserved with ordinary routine methods of urine examination.

It may, perhaps, be fair to compare Caiger's estimate, where those cases showing "a faint and transient cloud lasting less than three days" were omitted, with our cases in which casts were found. Such a table shows:

Caiger's statistics of the frequency of albuminuria in scarlet fever, 7.69 per cent.

Percentage of our cases of malarial fever in which albumin and casts were present, 17.5 per cent.

Despite these figures, and especially in view of McCollom's table, there can be little doubt that albuminuria is considerably more frequent in scarlet fever than in malaria.

Diphtheria. Assuming that McCollom's figures form a fair basis of comparison, we find:

Percentage of cases of albuminuria in malarial fever	46.4
" " " diphtheria	57.3

And this slight discrepancy in favor of diphtheria disappears when we consider æstivo-autumnal fever separately:

Percentage of cases of albuminuria in æstivo-autumnal fever . .	58.3
" " " diphtheria	57.3

Albuminuria, then, is more common in such notoriously severe acute infections as typhoid fever, scarlet fever, and diphtheria than in malaria; the difference, however, is by no means great. While occurring in only 38.6 per cent. of the regularly intermittent fevers, the frequency of albuminuria in æstivo-autumnal fever is probably fully as great as in diphtheria, and by no means so very much less than in typhoid and scarlet fevers.

Yellow Fever. While the occurrence of albumin in the urine in malarial fever cannot be compared in frequency with that observed in yellow fever, and while the amount, when present, is probably usually smaller, the fact that a majority of all instances of æstivo-autumnal fever in the climate of Baltimore, cases lasting but a short time and treated almost immediately by quinine, showed albuminuria, is strong presumptive evidence in favor of the idea that a considerably larger percentage of the severe pernicious cases which are most likely to be confounded with yellow fever must show this symptom. This would suggest caution in placing too great reliance upon the mere presence of albumin as evidence of the existence of yellow fever in a suspicious case.

It may be asked whether our figures represent the condition in the first days of an æstivo-autumnal infection. I think it may fairly be asserted that they do.

There were 96 cases of æstivo-autumnal fever in which the urine was examined within a week after the first symptoms of the infection. In the urine of these cases, albumin was present in 57, or 59.3 per cent., and casts were present in 28, or 29.1 per cent.

Acute Nephritis.

Among 1832 cases of malarial fever occurring in the Johns Hopkins Hospital and Dispensary we have observed 26 instances of acute

nephritis. In 3 of these instances there is room for possible doubt as to whether the nephritis may not have preceded the malarial infection, though in none is this believed to have been the case. There were:

Instances of	tertian fever	7
"	æstivo-autumnal fever	16
"	quartan fever	1
"	combined infection (tertian and æstivo-autumnal)	1
"	uncertain type	1
	Total	26

These were all typical cases of acute nephritis, the majority showing œdema, while abundant albumin and numerous casts and usually blood-corpuscles and epithelium were found in the urine.

In 14 instances the complication occurred in the first attack of malaria; in 11 the patient had suffered from one or more previous infections; in 1 there was no history obtainable.

In 13 instances the complication ended in recovery (Cases III., IV., V., VII., IX., X., XI., XII., XIII., XVIII., XIX., XXII., XXIV.).[1]

In 4 instances the complication ended in death (Cases I., II., XV., XVI.).

In 9 instances the result was doubtful (Cases VI., VIII., XIV., XVII., XX., XXI., XXIII., XXV., XXVI.).

Fatal Cases. The four fatal cases include the three instances in which some doubt may be held as to the true malarial nature of the case (Cases II., XV., XVI.).

In Case II. there was a history of œdema and bloody urine for several months, while regular chills had been noted but three weeks. The patient, however, had throughout this period been working in an extremely malarious district at the most dangerous time of the year. It is improbable that his malaria was acquired in December; far more likely that the infection occurred earlier in the season. He was a dull, stupid negro, and experience has shown us that a clear history of the time of onset of a malarial infection is often very difficult to obtain in such instances.

In Case XV. the clinical observation was unsatisfactory. Death

[1] In Cases III., IV., and V. there was still a trace of albumin present on discharge. In Cases XXII. and XXIV., dispensary patients, but one examination of the urine is recorded. In all instances, however, the general condition warranted the conclusion that the patients were on the road to definite recovery.

occurred in coma, the breath having a urinous odor and the urine containing one-fourth per cent. of albumin; the illness apparently began sharply with a malarial infection two weeks before. The record of the examination of the urinary sediment, however, was incomplete.

Case XVI. was one of characteristic acute nephritis which took on a chronic course, resulting fatally seven months after the onset. The patient had been living in a malarious district, and had had chills and fever for a month and a half before entry, associated with anasarca, ascites, and evidences of acute nephritis. Œdema of the feet, however, was said to have been noticed for a month before the onset of the chills. In this case there is a history of scarlet fever (without dropsy) six years before. It is our belief, in view of the absence of other causes, that all three of these instances were true malarial nephritis. It is but fair, however, to point to the possibility that another view of the matter may be taken.

In Cases XV. and XVI. autopsy was not permitted.

Case I. was an instance of pernicious fever in which death was due to the acute infection rather than to the nephritis. In Cases I. and II. the anatomical changes have been excellently described by Dr. Barker.

Histories of Four Fatal Cases.

Case I. *Pernicious malarial fever; æstivo-autumnal infection; acute nephritis; death; autopsy.*—No. 1769. J. B., male, aged thirty-four years, entered the hospital on September 10, 1890, complaining of fever, weakness, and headache. The patient has been sleeping on the ground in a very malarious district. For three days he has complained of great weakness and continuous vomiting. No further history is obtainable.

Physical examination. The patient is very weak and tremulous; tongue coated; thorax negative; spleen palpable; pulse 104; temperature 101°.

Blood. Æstivo-autumnal parasites; hyaline amœboid bodies in great numbers.

Sept. 11. The temperature rose this evening to 102°. No great change in the condition.

12*th.* The patient seems better to-day; vomiting is less frequent.

Treatment. Quinine, 0.325 (gr. v) three times a day.

On the 13th and 14th there was no vomiting, but the patient complained of great weakness. On the evening of the 15th the patient passed into a peculiar condition; he became drowsy and dull, and was aroused only with great difficulty; he was restless and uneasy, turning and tossing the clothes about; occasional vomiting. Throughout the night of the 15th the patient was restless and there was hiccough; the temperature, which had been nor-

mal since the 12th, fell to a subnormal point; the vomitus during the night was tinged with blood. On the morning of the 16th the patient was catheterized, 1500 c.c. of urine being obtained. The examination showed a specific gravity of 1010; a moderate quantity of albumin. The sediment contained many casts, chiefly granular and hyaline, though partly epithelial casts were not uncommon.

At 4 o'clock in the afternoon the temperature had fallen to 96°. The patient was very restless, cold, and dusky; growing steadily weaker and finally unconscious, he died at 8.45 P.M.

Autopsy. (Dr. Councilman.) Diagnosis: Pernicious malaria; acute splenic tumor; malarial pigmentation of spleen and liver; hypostatic congestion of the lungs. . . . "The kidneys were large and swollen, surface mottled, capsules adherent in places. On section the consistency is firm, the Malpighian tufts are prominent and congested. The medullary rays are pale, and betweem them the lines of vessels are deeply reddened. No areas of opacity are visible. The cortex is distinctly, though slightly, pallid." . . .

Microscopical examination by Dr. Barker:[1] "On microscopical examination all the bloodvessels of the kidneys were found to be dilated, the veins of the pyramids being especially wide. There is irregular dilatation of the glomerular capillaries. Comparatively few parasites are present in the kidneys, although some distinct forms are visible within the veins and capillaries. A number of phagocytic cells can be seen, intravascular phagocytes and endothelial cells. The capsules of some of the glomeruli have undergone fibrous thickening. In places the capsular endothelium is proliferated. The endothelium of the convoluted tubules is swollen and granular, and there are numerous hyaline casts to be seen in the small collecting tubules. In the pyramids hæmoglobin casts can be made out."

In this instance the nephritis, as in most cases of typhoid fever, played but a small part in the clinical picture of the disease. Possibly, had the patient recovered from the acute infection, or had life been further prolonged, clinical evidence of the renal changes might have appeared.

CASE II. *Malarial fever; double tertian infection; subacute nephritis; death three and a half months after onset.*—No. 5421. L. W., male, colored, aged twenty-three years; admitted January 9, 1893. Family and personal history negative. Gonorrhœa nine years ago. Three months ago, while working in a very malarious district, began to suffer from frequent micturition, general œdema, and bloody urine. For three weeks has had regular tertian chills.

Physical examination. Marked general œdema; ascites; no cardiac hypertrophy; pulse tension not increased; spleen not palpable (distended abdomen).

[1] Johns Hopkins Hospital Reports, 1895, v. 234.

Blood. The blood was not examined until after death; it then showed an extremely severe double tertian infection.

Urine. Dark amber; clear; acid; 1017; large amount of albumin. Sediment; hyaline, granular, and epithelial casts; many epithelial cells. There were daily febrile paroxysms, the nature of which was not appreciated during life. The urine ranged in quantity at first between 500 and 1000 c.c., diminishing gradually before death. For the last three days it amounted to but 260 to 350 c.c. The patient became enormously œdematous, and grew more and more anæmic. He was dull and stupid, but restless and uneasy. On January 26, 1893, he died.

The patient was treated throughout as a case of nephritis. A milk diet was ordered and frequent hot baths. Diuretin and digitalis were given internally.

Autopsy. (Dr. Councilman.) "*Anatomical diagnosis:* Acute malarial fever; double tertian infection; general streptococcus infection; subacute Bright's disease; malarial pigmentation of the organs; chronic passive congestion; general anasarca; infarctions of kidneys; erysipelas." . . .

"*The Blood.* Examined fresh from the peripheral veins and various internal organs showed enormous numbers of malarial parasites, most of them nearly full-grown; others only half-grown (tertian type), many of them enclosed within the protoplasm of large mononuclear leucocytes. . . ."

"The kidneys together weigh 400 grammes. They are both alike in size and general appearance. On the surfaces of each a few small fresh infarctions with hemorrhagic margins are visible. The capsules strip off easily. The general color of the external surfaces of the kidneys beneath the capsules is yellowish-brown, marked by scattered opaque darker areas, and here and there by minute hemorrhages. The whole kidney has a rather soft, œdematous feel. On section, the cortex has a yellowish appearance and is rather translucent; pyramids reddened, contrasting sharply with the lighter-colored cortex. In some parts of the cortex the striæ are well marked, in others they are less apparent or invisible. Average width of cortex 1 cm. A small amount of fluid exudes from the cortical substance on pressure. The glomeruli are indistinct. . . . Frozen sections of the *kidney* show a very little fat in fine droplets in the glomeruli. The epithelial cells of the tubules in the labyrinth are much swollen and are filled with fine albuminous granules and hyaline droplets. Many of the tubules are dilated and are lined by low epithelium. Casts are numerous in sections, and in urine collected from the bladder. Coagulated albumin is visible in the capsular spaces, in frozen sections made from a bit of kidney previously fixed in boiling water. The capsular epithelium is swollen and evidently proliferated. . . ."

The kidneys were carefully studied by Dr. Barker:[1]

"*The Kidney.* An examination of many glomeruli shows considerable variation in the size of the capsular spaces. While in some instances the glomerulus almost completely fills out Bowman's capsule, the space being a mere

[1] Johns Hopkins Hospital Reports, vol. v. p. 257.

chink, in others the latter is equal in size to one-third of the whole capsule. The space is not always empty, but may contain coagulated albumin, red blood-corpuscles and shadows, or a few mononuclear cells (desquamated epithelium). The fibrous capsules are not thickened except occasionally, where an atrophied glomerulus is visible. Frequently just outside the capsule of Bowman a narrow clear space can be made out, and this may contain a few cells, chiefly polynuclear leucocytes, or even be crowded with them. In many of the capsules the capsular epithelium is evidently proliferated, the whole inside of the space being lined by nuclei with intensely staining chromatin. The glomerular capillaries vary in their size and contents; some of them are empty, others are distended. Occasionally one is seen to be plugged with streptococci. The number of white corpuscles within the glomerular capillaries also varies; they are very irregularly distributed; in some glomeruli scarcely any are present; in others, one, two, or more of the glomerular capillaries may be packed full of polynuclear leucocytes. In a section stained in methylene-blue a capillary is visible plugged at one point with streptococci and crowded throughout the rest of its extent with leucocytes, with polymorphous nuclei—reminding one forcibly of the appearance of the capillary glass tubes in an experiment in positive chemotaxis. On the other hand, masses of cocci may be seen with no neighboring leucocytic accumulation. The nuclei of the polynuclear leucocytes vary in appearance: some stain sharply, and take on the ordinary forms; others stain less sharply, have a blurred look, and assume bizarre shapes. The protoplasm of the polynuclear leucocytes frequently contains granules or minute clumps of granules of malarial pigment, occasionally a well-formed parasite or short chains of cocci. There is some malarial pigment in the glomeruli contained within the protoplasm of mononuclear cells. The majority of the malarial parasites in the glomerular capillaries are outside nucleated cells. Here and there in specimens stained with aqueous magenta a giant spindle shaped nucleus is visible. The lumina of the convoluted tubules are for the most part wide, and are lined with rather low cubical epithelium. There are a few areas of dilated tubules in which the lining epithelium is flattened so as to resemble endothelium. The nuclei of the epithelial cells, as a rule, stain normally, although in some swollen cells they stain feebly, and in some tubules the nuclei are shrunken and the chromatin stains more intensely than normally.

Many of the convoluted tubules and collecting tubules contain hyaline casts; and hyaline droplets are visible within the swollen lining epithelial cells. These droplets, both the finer and the coarser, and the upper portions of the hyaline casts, stain intensely in Weigert's fibrin stain. Occasionally desquamated epithelial cells and a few red blood-corpuscles and round yellowish striped urinary concrements are to be seen within the lumina of the tubes.

The intertubular capillaries contain enormous numbers of streptococci (methylene-blue, Weigert's fibrin stain). Many of them are dilated and completely plugged with cocci, and sometimes chains of cocci are visible in

narrow pericapillary spaces. As in the glomerular vessels, some of the intertubular capillaries are crowded with leucocytes. Some of the small veins in the cortex are actually thrombosed with masses of streptococci, large numbers of malarial parasites, white corpuscles (some of which are necrotic), and pigment clumps. No bacteria other than streptococci are present anywhere in the kidney.

In the interstitial tissue of the kidney there is a slight but evident increase in the number of the cells of the lymphoid type. There are small nodal masses of smaller and larger round cells, usually with but little perinuclear protoplasm, many of them with fragmented nuclei. These minute nodes may contain, besides lymphoid cells, single polynuclear leucocytes or epithelioid cells.

Sections of the kidney treated with ferrocyanide of potassium and hydrochloric acid show an almost entire absence of cells containing hæmosiderin. Here and there, however, a little is visible within the protoplasm of the endothelium of the vessels.

The infarcted areas of the kidney present the lesions ordinarily seen under these circumstances—anæmic necrosis and neighboring reaction. The whole of the necrotic areas—glomeruli, tubules, bloodvessels, interstitial tissue—refuses to stain in the ordinary nuclear dyes, and has an increased affinity for eosin. The only nuclei which stain are those of polynuclear leucocytes which have invaded the interstitial tissue everywhere, and are accumulated in large numbers at the margins of the infarcted areas, and in the neighboring dilated bloodvessels. There is extensive nuclear fragmentation in these polynuclear leucocytes, and the most varied distortion-processes (*abschnürungsvorgänge*) of their nuclei are visible. Many of the bloodvessels at the apices and in the peripheries of these infarctions are thrombosed with streptococci, enormous numbers of malarial organisms, over 100 of which were counted inside the lumen of one vessel, and white cells. Small bits of the kidney hardened in Flemming's stronger solution and stained with aqueous magenta yield very instructive sections. Fine fat droplets are visible in the glomeruli and in the epithelium lining the capsular spaces. The convoluted tubules are not extensively fatty; some are entirely free from fat droplets, others show numerous smaller and larger droplets, especially at the proximal ends of the lining epithelial cells. Fine fat droplets are also visible in the protaplasm of some of the leucocytes in the vessels, and also in the smooth muscle fibres of the arteries. The desquamated epithelial cells within the lumina of the tubules contain numerous rather coarse fat droplets. The cells of the convoluted tubules in sections prepared in this way are seen to be finely granular, and the hyaline degeneration of the protoplasm is well shown. Many of them contain large vacuole-like spaces which sometimes displace the nuclei. In some of the tubes free red blood-corpuscles, polynuclear leucocytes, and malarial organisms are visible. The last named are sometimes free or lie on red blood-corpuscles; sometimes they are enclosed within cells. They are to be seen in both polynuclear and mononuclear cells

within the lumen of the convoluted tubules. In one tubule, besides numerous red blood-corpuscles and shadows, four free well-formed malarial organisms and a mononuclear cell containing within its protoplasm five malarial organisms of the same stage of development can be made out. Pictures such as these were seen too often to be accounted for by technical accidents. Occasionally red corpuscles, malarial parasites, and white cells are visible within the glomerular capsular spaces.

The time at which the streptococcus infection came on is not clear.

CASE XV. *Malarial fever; tertian infection; nephritis; uræmia; coma; death; no autopsy.*—No. 17,406. P. J., female, aged fourteen years; admitted September 26, 1896. The patient had chills and fever during six months last year. No history of other infectious diseases. Eleven days ago she began to suffer from pains in neck and legs, dyspnœa on exertion, fever, and cold sensations.

Physical examination. The face has a pasty white color; lips pale; tongue coated. The patient is very apathetic; somewhat delirious; spleen not palpable; no œdema; breath has a urinous odor.

Blood. Extra-cellular tertian bodies. Leucocytosis of 21,000.

Urine. Passed involuntarily, and lost.

Temperature. Subnormal.

On the 27th the patient became comatose.

Urine. Catheterized specimen: pale yellow; opaque; 1008; albumin ¼ per cent. The sediment contains considerable pus. No casts or blood to be seen.

Despite hypodermatic injections of quinine and stimulation, the patient died comatose on the 27th. Autopsy was not allowed.

This case is unsatisfactorily recorded. The author was absent at the time, but Dr. Camac, who saw the case, tells me that there is little doubt that the death was from uræmia.

As to the causal influence of the malaria there must be some question.

CASE XVI. *Malarial fever; æstivo-autumnal infection; acute nephritis, becoming chronic; death.*—No. 17,621. I. A., female, aged fourteen years, entered October 17, 1896. Family history negative. The patient had measles and whooping-cough as a child; scarlet fever six years ago. Has always been well and strong. She lives in a most malarious district. Two and a half months ago she began to notice slight œdema of feet and puffiness of eyes. A month and a half ago began to have chills and fever. At this time the swelling increased considerably, involving the genitalia and abdomen, and becoming very troublesome. The urine was reduced in quantity and red. There was marked pallor. The chills disappeared under treatment; she had but seven or eight in all, and thinks she has quite recovered from the malaria.

Physical examination. Marked pallor; general œdema and ascites. Heart's apex in fourth space, eight cm. from median line. Second aortic sound markedly accentuated.

Blood. Half-grown tertian parasites.

Urine. Pale; acid; 1012; albumin one-half per cent.; sediment abundant; epithelial cells, small round, and larger flat; hyaline, finely and coarsely granular casts; blood casts; pus cells; granular matter.

Under quinine the parasites rapidly disappeared. The temperature was normal. The urine, however, was always reduced in quantity and the œdema never cleared up. The pulse throughout was of high tension; second aortic sound markedly accentuated. Uræmic symptoms—headache, vomiting, and eventually coma—existed for five months, death occurring on March 20th. The albumin at times was present in as large quantities as 0.7 per cent. The patient was kept for the greater part of the time on a milk-diet; various diuretics and iron were given internally; hot-water and hot-air baths, with pilocarpine hypodermically, were given with only temporary effect. No autopsy was permitted.

Cases with uncertain result.

In nine instances (Cases VI., VIII., XIV., XVII., XX., XXI., XXIII., XXV., and XXVI.) the final outcome of the nephritis is not perfectly clear, though in the majority recovery probably occurred.

Cases XXIII., XXV., and XXVI. were observed in the dispensary, and were seen on but one occasion.

Case VI. was an instance of mild acute hemorrhagic nephritis occurring in æstivo-autumnal fever. The patient left a week after admission, feeling perfectly well, the urine, however, containing at the time of discharge a trace of albumin, while the sediment showed occasional hyaline and granular casts and red blood-corpuscles. There was no cardiac hypertrophy, no increase in the blood tension; never any œdema.

Case XIV. was that of a man, aged forty-one years, who had suffered off and on for a month with daily chills and for ten days with œdema of the face and extremities. The urine showed the characteristics of a mild acute hemorrhagic nephritis. Considerable improvement in the general condition occurred under quinine, but the patient had a carbuncle upon the back of the neck, and four days after entry left the hospital against advice, dreading an advised operation.

In Cases XVII., XX., and XXI., especially in the two former, there is some possibility that the process may have become chronic. These cases will be considered later.

GENERAL ANALYSIS OF 26 CASES OF ACUTE MALARIAL NEPHRITIS.

Age: From 1–10 years	. . . . .	2 cases.
" 10–20 "	. . . . .	4 "
" 20–30 "	. . . . .	9 "
" 30–40 "	. . . . .	6 "
" 40–50 "	. . . . .	5 "
Total	. . . . .	26 cases.

The figures in this table run practically parallel to those in our former statistics as to the relative frequency of malarial fever, with the exception of the slightly greater percentage of cases of nephritis between the ages of forty and fifty. The small percentage of cases under ten years of age is perhaps explained by the absence of a children's ward in the hospital.

Sex: Of the 26 cases there were: Males, 17 (65.3 per cent.); females 9 (34.6 per cent.).

Race: 20 of the 26 cases were in white patients (76.9 per cent.) and 6 in negroes (23 per cent.).

These latter figures are striking. Of 1832 cases of malarial fever but 82 (4.4 per cent.) were in colored patients; and yet of these few patients 6 (7.3 per cent.) developed acute nephritis, against 20 (1.1 per cent.) in 1750 whites.

These figures are quite in keeping with the clinical fact which we have learned to recognize, in this hospital at least—namely, that the colored race is more susceptible to renal disease than the white.

Relation of the Time of Development of the Nephritis to the Season of the Year.

TABLE SHOWING THE TIME OF DEVELOPMENT OF 26 CASES.

January	0	July	5
February	0	August	5
March	1	September	7
April	1	October	6
May	0	November	0
June	1	December	0—26.

It would thus appear that nephritis is much commoner at the height of the malarial season; rare in the early months of the year. Of these cases 11.5 per cent. only developed before July, while our statistics in

1712 cases as to the time of onset of the symptoms of malarial infection show that 17.1 per cent. develop during this period. The greater relative frequency of malarial nephritis in the second half year is clearly explained by its predominance in æstivo-autumnal fever.

Œdema was present in 19 of the 26 cases.

Blood was noted in the urine in 18 cases; it was absent in 7, while in 1 instance no note upon the sediment was made.

An exact estimate as to the *relative frequency* of nephritis in malaria is difficult to make. If we take into consideration the entire 1832 cases, it must be remembered that the urine was examined in the out-patient department in rare instances only, when the attention of the physician was definitely called to the possibility of some renal complication. And it is quite possible that cases of true nephritis may, under these circumstances, have escaped observation.

Among these 1832 instances of malarial fever there were 26 cases of acute nephritis, or 1.4 per cent.

The following table will show the *percentage of renal complications in the different types of fever:*

Regularly intermittent fevers (tertian and quartan) . .	1014 cases	—nephritis,	8 cases,	0.78	per cent.
Æstivo-autumnal fever . .	676 "	"	16 "	2.3	"
Combined infections . .	36 "	"	1 "	0.9	"

A more accurate estimate of the frequency of nephritis in malaria is probably to be obtained by a study of the cases observed within the hospital—758 in number. The objection might be raised that these cases were, as a rule, somewhat more severe than those observed in the dispensary. But, inasmuch as all patients presenting themselves at the dispensary with malaria are recommended for admission, many of the mildest cases entering, this objection is probably not as important as it might appear at first. It is probably safe to say that the figures obtained from the house-cases, while doubtless somewhat too high, are less out of the way than those obtained from a consideration of the total number.

Among the 758 cases of malarial fever treated in the Johns Hopkins Hospital there were 21 instances of acute nephritis of probably malarial origin, or, in other words, 2.7 per cent. In three of these instances there is room for some doubt as to whether, possibly, the

infection may not have occurred after the beginning of the nephritis. Leaving out these possible doubtful cases, we are then left with a percentage of 2.3 of acute nephritis.

The frequency of acute nephritis in æstivo-autumnal fever was, as might have been expected, far greater than in the regularly intermittent fevers.

In 394 cases of tertian and quartan fever there were 6 instances of nephritis (1.5 per cent.), or, if we omit the 3 cases in which there is some doubt as to the etiology of the nephritis, 3 instances (0.7 per cent.).

Among 296 cases of æstivo-autumnal fever there were 14 instances of acute nephritis (4.7 per cent.).

Out of 26 instances of combined infections there was 1 case of acute nephritis (3.5 per cent.).

A comparison of these statistics with those of other observers in other acute infections is interesting.

a. Typhoid Fever. Among 389 cases of typhoid fever we have had 14 instances of acute nephritis,[1] or 3.6 per cent. In none of these cases, however, was œdema present, and in none of the fatal cases was death apparently due to the renal complication. Complete recovery occurred in all instances which did not die from other complications of typhoid fever.

b. Scarlet Fever. The most satisfactory statistics are those of Caiger,[2] who observed, among 4015 cases of scarlet fever in the London Fever Hospital, 3.31 per cent. of instances of acute nephritis, a percentage but little higher than that observed by us in all varieties of malaria—2.7 per cent.

c. Diphtheria. In diphtheria the frequency of true acute nephritis is difficult to estimate.

Trousseau[3] observed dropsies in barely 5 per cent. of his cases; Sanné,[4] in 7 (3.1 per cent.) out of 224 instances in which albuminuria was present, or in 1.7 per cent. of all his cases. In our cases of

[1] The determination of what shall be called clinically "acute nephritis" is necessarily somewhat arbitrary. Among our cases, in the absence of gross clinical evidence of renal disturbance, we have included only those where the urine showed a large quantity of albumin with numerous casts—or, if the albumin were not especially abundant, where the sediment showed, in addition to casts, blood and renal epithelium. We have, for this reason, omitted from our typhoid statistics some of the cases classed by Hewetson as nephritis.

[2] Op. cit.

[3] Quoted from Barthez and Sanné, op. cit., p. 457.

[4] Traité de la diphthérie, 8vo, Par., 1877.

malaria, dropsy was present in 4.6 per cent. of the cases in which there was albuminuria, or in 1.9 per cent. of all our cases.

From McCollom's valuable statistics nephritis would appear to be an unimportant complication of diphtheria. But 5.2 per cent. of 633 cases had over 0.1 per cent. albumin in the urine, while œdema was noticed in but 4 instances. "In the 71 autopsies, in no instance was the condition of the kidneys such as to have materially contributed to the fatal issue."

It may then be seen that while albuminuria is more common in typhoid fever than in malaria, true acute nephritis, with general dropsy and other characteristic symptoms, is apparently of greater frequency in the latter affection. And while malarial fever cannot be said to exercise as deleterious an influence upon the kidneys as does scarlet fever, the percentage of acute nephritis among our cases of malaria is more than half as large as that of Caiger in scarlet fever.

Considering the different types of malarial affection separately, these facts are more strikingly brought forth. The percentage of cases of acute nephritis in our 296 instances of æstivo-autumnal fever is higher than that in any of the above-mentioned infections.

TABLE.

Percentage of cases of nephritis in æstivo-autumnal fever . . .	4.7
" " " typhoid fever	3.6
" " " scarlet fever (Caiger) . . .	3.5

In comparison to Sanné's estimate that 3.1 per cent. of the albuminurias in diphtheria have dropsy, we have the fact that out of 165 cases of albuminuria in æstivo-autumnal fever 9, or 5.4 per cent., showed this symptom.

In view of these figures it is difficult to escape the conclusion that malarial fever is one of the acute infections in which acute nephritis is comparatively common. This is especially true of æstivo-autumnal infections where its frequency, if not its severity, would, from our statistics, appear to be equal to that of scarlet fever, typhoid fever, or diphtheria.

The important rôle which malarial fever plays in the etiology of acute nephritis in Baltimore is testified to by the fact that out of 112 instances of acute nephritis observed in the Johns Hopkins Hospital 21, or 18.7 per cent., were of malarial origin.

All observers agree that there is a great difference in the malig-

nancy of different infections, and our statistics would lead us to recognize the justice of this observation. Fifteen of our 26 instances of malarial fever occurred during the summer and fall of 1896, at a time when an unusually large amount of severe malarial fever prevailed.

It is not improbable that the especial malignancy of this epidemic of 1896 may account for the rather strikingly high percentage of instances of nephritis which have come under our observation.

Our statistics would lead us to assume that this complication is more frequent than it would appear to be in Rome from the observations of Rem-Picci.

Chronic Nephritis.

What influence, if any, may malarial fever have upon the development of chronic nephritis?

In four instances of acute nephritis observed in the hospital there is some reason to believe that the process may have assumed a chronic course. The first (Case XVI.) has already been mentioned among the fatal cases (page 356). The patient died, after an illness lasting from six to seven months, with the symptoms of a chronic diffuse nephritis. An autopsy was not permitted. It will be remembered that there was some question in this case as to whether the malaria might not have been a secondary infection developing in a patient already suffering from nephritis. The time of onset of the trouble, the surroundings of the patient, the absence of other etiological elements, make it highly probable that the malarial infection was the primary cause of the disease.

Case XVII. *Malarial fever; double tertian infection; chronic nephritis; little improvement.*—No. 17,836. A. T., female, colored, aged twenty-one years. Admitted November 10, 1896. Family and personal history good; no history of other infectious diseases. The patient suffered in September with chills and fever, which disappeared after treatment with quinine for one week, when she believed that she had completely recovered from the infection. For four weeks she has suffered with œdema of the back and legs, abdominal pain, headaches, cough, and dyspnœa. Two days ago had a chill.

Physical examination. Marked pallor; general œdema and ascites; right hydrothorax.

Heart. Apex in fifth space 12½ cm. from the median line; no accentuation of the second aortic sound. Spleen not palpable.

Blood. Tertian parasites.

Urine. Smoky; 1025; acid; albumin abundant, nearly 1 per cent. Sediment abundant; leucocytes; vaginal epithelial cells; occasional decolorized

red blood-corpuscles; numerous hyaline and finely granular casts; some coarsely granular casts, many having small round cells adherent; occasional blood and epithelial casts.

There were slight febrile paroxysms on the 10th and 11th. Under treatment with quinine the temperature became normal on the 13th, and remained so thereafter.

The patient was placed on a milk diet, given diuretics (diuretin, bitartrate of potassium) and iron (Blaud's pills). Frequent hot baths, with and without the addition of pilocarpine hypodermatically, were given to induce sweating.

The urine, reduced in amount for the first several days, was normal or slightly increased in quantity thereafter. The specific gravity varied between 1025 on entrance and 1008 on December 2d. For the three weeks before discharge it averaged about 1010. The blood disappeared from the urine by the 18th of November, but returned again on the 21st. On the 5th of December the patient left against advice, still œdematous, the urine showing $\frac{1}{8}$ per cent. albumin.

In this instance the duration of the case (two and a half months); the persistence of the symptoms, and the continued large quantity of albumin, led us to believe that we were dealing with a chronic diffuse nephritis. Unfortunately, we have been unable to learn the subsequent history of the case.

CASE XX. *Malarial fever; æstivo-autumnal infection; acute hemorrhagic nephritis; recovery* (?).—No. 20,905. C. B., colored, aged twenty years. Admitted October 12, 1897. Family history negative. Measles, whooping-cough, and chicken-pox as a child. The patient has suffered for a month with daily and tertian chills. He has been taking quinine, and has had no chills for five days. Two weeks ago œdema of the legs and feet appeared, and a week later became general. The urine has been of a dark color.

Physical examination. Pallor; general anasarca; point of maximum cardiac impulse in the fourth space 10 cm. from the median line; pulse of rather high tension; spleen not palpable.

Blood. Æstivo-autumnal parasites, pigmented ovoid forms.

Urine. Yellow; acid; 1017; albumin 0.4 per cent.; sediment; many uric-acid crystals; many granular, hyaline, and epithelial casts.

There were slight daily febrile paroxysms from the 15th to the 20th, on which date treatment with quinine, 0.325 (gr. v) every four hours was begun; the temperature reached normal by the 23d.

The patient was given a milk diet and bitartrate of potassium as a diuretic. Later, iron in the form of Blaud's pills was given.

On the 23d the urine suddenly became smoky, containing red blood-corpuscles; it was somewhat reduced in quantity from the 23d to the 30th, after which time it was steadily above the normal amount, sometimes passing 3000 c.c. The albumin gradually diminished in quantity. The œdema and ascites had disappeared by the 26th. There was no evidence of albuminuric retinitis. There was no cardiac hypertrophy, the point of maximum impulse being in the fifth space 8.8 cm. from the median line just before discharge. A slight trace of albumin, however, still remained present in the urine.

On the 23d the patient left the hospital with a trace of albumin yet in the urine, and a few hyaline, granular, epithelial, and blood casts still present.

The patient has been heard from repeatedly since his departure. He believes himself to be well. A specimen of *urine* obtained several weeks ago (April 18, 1898) had a specific gravity of 1018. There was a very faint trace of albumin. Microscopically, a few red blood-corpuscles were found in a centrifugalized specimen as well as one or two coarsely granular casts. From the patient's letter there would appear to have been a moderate polyuria.

CASE XXI. *Malarial fever; æstivo-autumnal infection; acute hemorrhagic nephritis; recovery* (?).—No. 20,981. C. K., male, aged thirty-one years. Admitted October 20, 1897. Family history negative. Had measles as a child and diphtheria (?) at thirteen. For twenty days the patient has had quotidian chills and fever, off and on, relieved at times by quinine. Two days ago the legs became œdematous, and there was dyspnœa on exertion. The urine was of a reddish color.

Physical examination. Pallor; general anasarca; no cardiac hypertrophy; spleen not palpable.

Blood. Æstivo-autumnal parasites; hyaline amœboid bodies.

Urine. Reddish brown; smoky; 1015; acid; albumin 0.4 per cent.; sediment abundant; numerous hyaline, epithelial, granular, and blood casts; red blood-corpuscles, normal and decolorized; epithelial cells.

There was irregular fever for forty-eight hours.

Treatment with quinine was begun on the 21st, and the temperature was normal by the 23d. The patient was given a milk diet and bitartrate of potassium as a diuretic. Later, tr. ferri chloridi, 1 3 (♏xx) t. i. d., was also given. The œdema slowly disappeared, remaining absent after November 15th.

The *urine*, only 700 c.c. in amount on October 21st, and 1290 on 22d, was afterward continually increased in quantity, the amount at times passing 2500 c.c. The albumin diminished rapidly, but was still present as a trace on discharge. No blood appeared in the sediment after December 24th.

The pulse tension was rather high, and the second aortic sound was somewhat accentuated, but no retinal changes were to be made out.

The patient was discharged at his own request on January 24, 1898, feeling quite well. The *urine* on this date was clear, acid, 1010. There was a trace of albumin. The sediment still showed a few granular casts.

In both of these instances there is some question as to whether or not the renal changes have assumed a chronic course. In Case XX. the presence of blood and an occasional cast in the urine six months after the onset of the affection, testifies to the gravity of the lesions produced by the acute infection while in Case XXI. the high blood tension and the persistence of albumin and casts were suspicious of a chronic change.

Case XVII. represented, apparently, a true chronic malarial nephritis, and, in view of the literature above quoted, there can be but

little doubt as to the existence of such cases. Although unable to present any further instances than these mentioned in support of such a view, it is, I think, safe to assume that any infection, the toxicity of which is sufficient to produce as large a percentage of serious acute nephritides as malarial fever, must play a certain part in the etiology of chronic renal changes.

It may probably be considered as a generally recognized fact that scarlet fever, diphtheria, and typhoid fever result sometimes in changes in the kidneys which may lead secondarily to grave chronic nephritis. And such changes are generally supposed to be due to circulating toxic substances, produced either directly by the growth of the infectious organisms, as in diphtheria, or set free from the bodies of the dead bacteria, as in typhoid fever, or resulting secondarily from the action of such substances on the fluids and tissues of the body.

The surprising frequency of acute nephritis in our cases of malarial fever would appear to be an indication of the extreme toxicity of the circulating poisons present, evidence of the existence of which has been previously brought forward in the grave changes noted by Guarnieri,[1] Bignami,[2] Barker,[3] Monti,[4] and others in the spleen, liver, and brain. Does it not, perhaps, justify us in considering seriously whether, after all, repeated and chronic malarial infections may not play a greater part in the development of chronic renal changes than we have previously been in the habit of assuming?

Summary.

In 758 cases of malarial fever treated in the wards of the Johns Hopkins Hospital albuminuria occurred in 46.4 per cent. and casts of the urinary tubules in 17.5 per cent.

Albuminuria was much more frequent in æstivo-autumnal fever than in the regularly intermittent fevers, occurring in but 38.6 per cent. of the latter and in 58.3 per cent. of the former, while casts of the renal tubules were found in 12.2 per cent. of tertian and quartan infections and in 24.7 per cent. of the cases of æstivo-autumnal fever.

The frequency of albuminuria in æstivo-autumnal fever is apparently equal to that in diphtheria, though less than in scarlet and typhoid fevers.

Out of 1832 cases of malarial fever in the hospital and in the out-

[1] Atti d. R. acc. med. di Roma, 1897, s. ii., iii., 247.
[2] Ibid., Anno xvi., 1890, s. ii., v. 317.
[3] Johns Hopkins Hospital Reports, 1895, v. 220.
[4] Bull. d. Soc. med.-chir. d. Pavia, 1895.

patient department there were 26 instances of nephritis of malarial origin, or 1.7 per cent. Of these, 13 recovered, 4 died, and in 9 the result was doubtful, 3 instances probably becoming chronic. In 3 of the fatal cases there is possible doubt as to the malarial nature of the case.

Nephritis occurs apparently in from 1 to 2 per cent. of all cases of malarial fever in the neighborhood of Baltimore. The complication is more frequent and severe in æstivo-autumnal fever; it is commonest during the height of the malarial season, in July, August, September, and October; it is rare in the first half of the year.

The relative frequency of malarial nephritis appears to be much greater in the negro than in the white race.

There is nothing especially distinctive in the clinical characters of the disease. It shows the usual features of an acute toxic nephritis; the tendency is apparently toward a short course and a favorable issue. Severe fatal or chronic forms of the disease may, however, occur, two, possibly four, instances of chronic nephritis of malarial origin having come under our observation.

Conclusions.

1. Albuminuria is a frequent occurrence in the malarial fevers of Baltimore, occurring in 46.4 per cent. of our cases.

2. It is considerably more frequent in æstivo-autumal infections, occurring in 58.3 per cent. of these instances, against 38.6 per cent. in the regularly intermittent fevers.

3. Acute nephritis is a not unusual complication of malarial fever, having occurred in over two per cent. of the cases treated in the wards of the Johns Hopkins Hospital, and in between one and two per cent. of all cases seen at the institution.

4. The frequency of acute nephritis in æstivo-autumnal fever is much greater than in the regularly intermittent fevers, having been observed in 4.7 per cent. of the cases treated in our wards, and in 2.3 per cent. of all the cases seen.

5. The frequency of albuminuria and nephritis in malarial fever, while somewhat below that observed in the more severe acute infections, such as typhoid fever, scarlet fever, and diphtheria, is yet considerable.

6. There is reason to believe that malarial infection, especially in the more tropical countries, may play an appreciable part in the etiology of chronic renal disease.

CASES.

CASE I.—*Vide* page 351.

CASE II.—*Vide* page 352.

CASE III. *Æstivo-autumnal malaria; acute hemorrhagic nephritis; recovery*—No. 8126. L. S., aged thirty-one years, was admitted September 6, 1893. Family history negative; had measles as a child. The patient lives in a very malarious district, and had chills and fever three years ago. A week before entry began to complain of œdema of the legs, dyspnœa, and cough with tenacious mucous expectoration.

Physical examination. Marked pallor; moderate œdema of the legs; fine moist râles at the bases of both lungs; no cardiac hypertrophy; pulse of normal tension; spleen palpable.

Blood. Æstivo-autumnal parasites; hyaline amœboid bodies and crescents.

Urine. Dark reddish-brown; opaque; acid; 1021; much albumin. Sediment: very numerous hyaline, granular, epithelial, and blood-casts; red blood-corpuscles, normal and decolorized; leucocytes; epithelial cells.

There were paroxysms of fever on the afternoons of the 7th and 8th; the fever rapidly disappeared under quinine, which was begun upon the 8th. On the 9th and 10th the patient was given four doses of quin. et ureæ muriatis, 0.65 (gr. x), hypodermatically. The albumin, at first nearly ½ per cent., rapidly diminished to a faint trace on October 18th. No casts were to be found in the sediment after September 30th. The quantity of urine, at first diminished, was always above the normal after September 14th. On October 23d the patient was discharged, feeling perfectly well; the urine, however, still showed a faint trace of albumin. Beyond the quinine, which was administered in doses of 0.325 (gr. v) every four hours from September 9th to 23d, and afterward in doses of 0.325 (gr. v) three times a day, the patient received no medicinal treatment.

CASE IV. *Malarial fever; mixed æstivo-autumnal and tertian infection; acute nephritis; recovery* (?).—No. 8302. J. J., aged thirty years, was admitted October 2, 1893. Family history negative; always healthy, except for an attack of malaria two years ago. For two weeks daily chills, headache, vomiting; for two days œdema of the hands and feet and vertigo

Physical examination. Sallow color; marked pallor; moderate general œdema; arteries slightly thickened; no cardiac hypertrophy; no accentuation of second aortic sound; spleen palpable.

Blood. Mixed infection; æstivo-autumnal and tertian parasites, the former in excess.

Urine. Reddish-amber; clear; acid; 1022; distinct trace of albumin. Sediment: granular and epithelial casts, many cylindroids, few leucocytes.

There were paroxysms of fever on the 2d, 3d, and 4th.

Treatment. Quinine 0.65 (gr. x) every four hours on the 2d, 3d, and 4th, and 0.325 three times a day from the 10th on.

The temperature, which had shown daily elevations, was normal after October 4, 1893. October 6th. Urine: dark-yellow; acid; 1015; trace of

albumin; many large epithelial and hyaline casts, some with blood adherent; few red blood-corpuscles; few leucocytes. The patient was discharged, apparently well, on the 12th. There was no final note upon the urine.

CASE V. *Æstivo-autumnal infection; acute hemorrhagic nephritis; possible exacerbation of a chronic nephritis; recovery* (?).—No. 8558. F. L., male, aged thirty-eight years, was admitted November 4, 1893. Family history negative; measles as a child; typhoid fever fourteen years ago; smallpox eight months ago. Has had tertian chills off and on for four weeks, relieved occasionally by quinine. For two weeks there have been œdema of the feet and legs, dyspnœa, headache, frequent micturition, and ischuria.

Physical examination. Pallor; marked œdema of the legs; breath urinous; heart slightly hypertrophied; apex impulse in the sixth space just outside the mamillary line; second aortic sound accentuated; radial tension somewhat increased; artery not thickened; spleen palpable.

Blood. Æstivo-autumnal parasites; hyaline, amœboid bodies, and crescents.

Urine. Smoky; acid; 1015; albumin, 0.4 per cent. Sediment: numerous hyaline and granular casts; epithelial casts; red blood-corpuscles; round epithelial cells; few leucocytes.

There was slight fever on November 4th and 5th, disappearing immediately under treatment with quinine 0.325 (gr. v) every four hours, which was discontinued on the 15th. The patient was placed on a milk-diet and given frequent hot-air baths. For five days the quantity of urine varied between 500 and 1200 c.c., after this date being above the normal quantity. The albumin rapidly diminished in amount, the œdema at the same time disappearing. On the 18th a faint trace of albumin was present and a few granular casts; a few red blood-corpuscles were still to be found. On the 23d the patient was discharged, apparently well.

CASE VI. *Æstivo-autumnal malarial fever; acute hemorrhagic nephritis; recovery* (?).—No. 13,578. J. T., aged twenty-one years, was admitted August 13, 1895. Family history good; no previous illness beyond an attack of chills and fever two years ago, lasting three weeks. For three weeks has had daily chills and pain in the head and abdomen.

Physical examination. Marked pallor; no cardiac hypertrophy; no increase in pulse tension; spleen palpable.

Blood. Æstivo-autumnal parasites; hyaline bodies and crescents.

Urine. Smoky; acid; 1012; trace of albumin. Sediment: dark-brown, flocculent, showing microscopically blood and pus cells, and hyaline and granular casts with blood adherent.

There were febrile paroxysms on the 13th and 14th, disappearing immediately under quinine, which was begun on the 14th—0.65 (gr. x), two doses, and then 0.325 every four hours. The urine increased in quantity; the albumin diminished, but was still present as a trace, with occasional hyaline, granular casts, and red blood-cells in the sediment on the day of discharge. On August 19th the patient, feeling perfectly well, left against advice. Beyond quinine, iron, in the form of Blaud's pills, was the only medicinal treatment.

CASE VII. *Malarial fever; æstivo-autumnal infection; cachexia; acute nephritis; recovery.*—No. 14,527. M. J. M., female, aged twenty-nine years. Admitted November 18, 1895. Family history negative. Scarlet fever, with dropsy, seventeen years ago; syphilis two years ago; otherwise always well and strong. Chills and fever, her first attack, off and on for seven months; frequent headaches; general debility. For three weeks moderate œdema of the face and legs.

Physical examination. Marked anæmia (1,160,000 red corpuscles) and cachexia. *Heart.* Apex just outside nipple in fifth space; soft blowing murmur all over cardiac area, lost in the axilla; no increase in pulse tension; spleen much enlarged.

Blood. Æstivo-autumnal parasites; hyaline bodies, crescentic and ovoid forms.

Urine Cloudy; acid; 1006; decided trace of albumin; heavy brownish precipitate. Microscopically, numerous pus cells and granular casts with epithelial cells adherent.

There was irregular fever on the 18th and 19th, disappearing rapidly under quinine, 0.325 (gr. v), three times a day. The diet was restricted, and iron in the form of Blaud's pills was given.

The *urine* was increased in quantity throughout, and showed always a trace of albumin with a sediment as above, excepting for the occasional presence of a few red blood-corpuscles.

The œdema disappeared, and on December 10th the patient left the hospital against advice, feeling greatly improved.

On January 27, 1896, patient returned complaining of severe nocturnal headaches which were of luetic origin, and disappeared in two weeks under iodide of potassium. The anæmia was much improved; red blood-corpuscles 3,300,000.

Urine. Somewhat increased in quantity; still contains about 0.5 per cent. of albumin. The sediment showed hyaline and granular casts with occasional epithelial cells adherent.

The patient was again in the hospital in April, 1898, suffering from syphilitic periostitis. The *urine* throughout was normal; excretion of solids and urea normal; no albumin; no polyuria.

CASE VIII. *Malarial fever; obstinate quartan infection; acute nephritis; recovery* (?).—No. 16.720. R. M., aged twenty-two years, colored. Admitted July 19, 1896. Family history negative. Measles and whooping-cough as a child. Lived in a malarious district; has had chills and fever off and on for many years, more or less steadily for a year. For several months there has been frequent micturition, for four weeks œdema of feet and legs.

Physical examination. Marked pallor; no cardiac hypertrophy; no increased pulse tension; spleen palpable.

Blood. Triple quartan infection.

Urine. Pale yellow; neutral; 1010; albumin abundant; sediment; few leucocytes and red blood-corpuscles; hyaline casts.

The paroxysms, quartan in character, disappeared rapidly after quinine,

0.325 (gr. v), every four hours, which was begun on the 24th. The œdema rapidly diminished, and had entirely disappeared on discharge, excepting for a slight puffiness about the eyes. The *urine* throughout was increased. The albumin and casts rapidly diminished in quantity, but there was still a trace of the former on discharge.

The patient left against advice on July 30th, considering himself well. Besides quinine, the only medicinal treatment was with iron in the form of Blaud's pills.

CASE IX. *Malarial fever; æstivo-autumnal infection; acute hemorrhagic nephritis; recovery.*—No. 16,832. W. E., colored, male, aged forty-two years. Admitted July 30, 1896. Family history negative. Measles, mumps, and whooping-cough as a child; pneumonia twenty-four years ago. For nine days, weakness, nausea, exhaustion. Syncopal attack two days ago; ischuria; frequent micturition.

Physical examination. Color good; tongue coated; no cardiac hypertrophy; apex impulse in the fifth space within the nipple line; no increase in pulse tension; spleen not palpable.

Blood. Æstivo-autumnal parasites; hyaline, amœboid, and ring-shaped forms.

Urine. Deep red; acid; 1030; marked trace of albumin; sediment, considerable; pus and red blood-corpuscles; hyaline and granular casts; small, round epithelial cells.

There were febrile paroxysms on the 30th and 31st, which disappeared immediately under quinine, 0.325 (gr. v), every four hours. The patient left the hospital apparently well on August 8th. There was no marked polyuria. Unfortunately, no further record was made of his urine.

The patient was seen again on April 16, 1898. Has been perfectly well since discharge. Is convalescent from a mild attack of acute bronchitis.

Heart's apex in sixth space 10 cm. from the median line, about in the mammillary line. Pulse tension not increased. Radial artery very slightly thickened.

Urine, passed at 11 A.M.; high color; acid; 1026½; no albumin by nitric acid or heat. Sediment; numerous cylindroids; small round cells; *occasional red blood-corpuscles; a few hyaline casts with an occasional degenerated cell adherent.*

CASE X. *Malarial fever; æstivo-autumnal infection; acute hemorrhagic nephritis; recovery.*—No. 16,995. A. H., male, aged thirty-five years. Admitted August 13, 1896. Family history negative. Measles, scarlet fever, and small-pox in childhood; renal colic nine years ago. Has complained for three days of severe headache, general exhaustion, and fever; has never had malarial fever previously.

Physical examination. Patient has high fever; is flushed; tongue coated; no cardiac hypertrophy; no increase in blood tension; spleen palpable.

Blood. Æstivo-autumnal parasites; hyaline amœboid bodies.

Urine. Dark; smoky; 1030; acid; trace of albumin; sediment slight. Microscopically, red blood-corpuscles, granular and hyaline casts.

There was high continued fever from the 13th to the 16th, after which date the temperature was normal following treatment with quinine, 0.325 (gr. v), every four hours, which was begun on the morning of the 14th.

The patient left on the 18th, feeling well. Unfortunately, no further note was made upon the urine.

The patient has been seen on a number of occasions since that time. Has had no further attacks of malaria, and believes that he is in perfectly good health. A specimen of urine obtained in June, 1898, was quite normal.

CASE XI. *Malarial fever; æstivo-autumnal infection: acute nephritis; recovery.*—No. 17,000. J. P., female, colored, aged forty-four years. Admitted August 13, 1896. Family history negative. Measles, mumps, and whooping-cough as a child. Has had several previous attacks of chills and fever. For about two weeks has complained of vomiting, headache, and at times slight delirium; ischuria.

Physical examination. Large woman; tongue coated; no anasarca; fine râles at bases of the lungs; slight accentuation of second aortic sound; no apparent cardiac hypertrophy; no increased pulse tension; spleen not palpable.

Blood. Æstivo-autumnal parasites; amœboid hyaline bodies and crescents.

Urine. Amber; acid; 1025; albumin 0.2 per cent. Sediment: pus and vaginal epithelium, hyaline and granular casts.

There were febrile paroxysms on the 13th, 14th, and 15th, disappearing rapidly under quinine. The patient left the hospital on August 22d, at her own request, feeling perfectly well. Unfortunately, no final note was made upon the urine.

The patient was communicated with by letter, and states on April 10, 1898, that she is perfectly well. She has, however, had chills and fever since leaving the hospital. A specimen of urine obtained in May, 1898, was absolutely normal in character.

CASE XII. *Malarial fever; æstivo-autumnal infection; nephritis; recovery.*—No. 17,071. C. S., aged twenty-seven years; male. Admitted August 21, 1896. Family history negative. Has had no serious illness. The patient never suffered from malarial fever previously; he lives in a malarious district. Seven weeks ago began to suffer with swelling of the abdomen and legs, for which he took to bed. Since then the swelling has become general.

Physical examination. Yellowish complexion; marked pallor; no cardiac hypertrophy; slight accentuation of the second aortic sound; spleen palpable; marked œdema of the legs.

Blood. Æstivo-autumnal parasites; numerous crescentic and ovoid forms.

Urine. Light amber; 1012; trace of albumin; numerous hyaline and granular casts with epithelium adherent; epithelial casts; yellow granular casts, suggestive of a blood staining.

There was moderate fever on admission, rapidly disappearing under quinine, 0.325 (gr. v), every four hours, which was begun on August 23d. The patient was placed on a milk diet and given bitartrate of potassium as a diuretic.

The quantity of urine up to September 11th was above normal, averaging over 2000 c.c., the albumin diminishing in quantity. Occasional blood-corpuscles were also seen in the sediment and upon the casts.

On the 16th, without apparent cause, the urine fell to 600 c.c. There were pain and swelling of the left knee-joint.

17th. Urine reddish; smoky; albumin 0.15 per cent. Sediment, numerous blood-corpuscles and an increased number of casts.

From this date the urine steadily improved, the quantity being throughout supranormal. The patient improved progressively; the swelling and pain in the knee rapidly disappeared.

Oct. 21st. Urine: 3000 c.c.; pale; acid; 1010; no albumin; sediment shows nothing abnormal. Patient discharged well.

CASE XIII. *Malarial fever; æstivo-autumnal infection; acute hemorrhagic nephritis; recovery.*—No. 17,250. M. S., female, aged ten years. Admitted September 9, 1896. Family history negative. Has had measles. Lives in a malarial district, and has had chills before. One week ago she began to have fever, abdominal pain, and headache. There were two chills at the onset; these were followed by swelling of the abdomen and legs.

Physical examination. Marked pallor; general œdema and ascites. No cardiac hypertrophy; blood tension not increased; spleen palpable.

Blood. Æstivo-autumnal parasites; crescentic forms.

Urine. Smoky; acid; 1015; 0.2 per cent. albumin. Sediment, pus, hyaline, granular and blood casts; red blood-corpuscles.

There were febrile paroxysms on the 10th, 11th, and 12th, disappearing immediately after quinine, 0.26 (gr. iv), three times a day, on the 13th. The patient was given a milk diet, and bitartrate of potassium as a diuretic.

The œdema slowly disappeared. It was last noted on the 29th of September. The urine, at first reduced in quantity, soon became increased above the normal amount; the albumin diminished to a slight trace.

Oct. 24th. Urine pale; acid; 1012; albumin 0.1 per cent. Sediment, few granular and hyaline casts; several red blood-corpuscles.

Oct. 25th. The patient was discharged to-day feeling perfectly well.

See subsequent history, Case XVIII.

CASE XIV. *Malarial fever; æstivo-autumnal infection; acute hemorrhagic nephritis; carbuncle; left the hospital improved.*—No. 17,266. H. J. S., aged forty-one years. Admitted September 11, 1896. Family history good. Measles as a child; syphilis eight years ago; malaria seven years ago.

The patient has had daily chills off and on for a month, the last twelve days ago; this is his first attack. Ten days ago, after exposure, œdema of the face and extremities appeared. Afterward he began to suffer with pain in the neck.

Physical examination. Marked pallor; general œdema; ascites; no cardiac hypertrophy; carbuncle on the back of the neck; heart sounds normal; arteries slightly thickened; spleen not palpable.

Blood. Æstivo-autumnal parasites; hyaline bodies; presegmenting forms; crescentic bodies.

Urine. Dark red; acid; 1017; albumin abundant. Sediment, heavy, brownish; granular, epithelial, blood, and pus casts; epithelial cells; leucocytes; red blood-corpuscles.

There were slight evening elevations of the temperature on the 11th, 12th, and 13th. On the 14th the patient left the hospital against advice; operation upon the carbuncle having been advised. The patient was much improved, the œdema having almost disappeared.

CASE XV.— *Vide* page 356.

CASE XVI.— *Vide* page 356.

CASE XVII.— *Vide* page 362.

CASE XVIII. *Malarial fever; double tertian infection; acute hemorrhagic nephritis; recovery.*—No. 19,288. M. S., female, aged eleven years. Admitted April 27, 1897. The patient, who had suffered from a similar attack in September, 1896 (Case XIII.), had been enjoying good health since her discharge from the hospital.

Seventeen days ago she began to have tertian chills, which have continued since. There have been frequent attacks of nausea and vomiting and vertigo.

Physical examination. Marked pallor; face puffy; heart and lungs negative; spleen palpable.

Blood. Two groups of tertian parasites.

Urine. Smoky; acid; 1015; trace of albumin. Sediment, moderate; small epithelial cells, hyaline and granular casts, one with a considerable quantity of fat; few leucocytes; occasional red blood-corpuscles. Febrile paroxysms occurred on the 27th and 28th, disappearing after treatment by quinine, 0.13 (gr. ii), every four hours.

The patient improved rapidly, the smokiness disappearing soon from the urine. The œdema of the eyes rapidly subsided.

May 4th. Urine. Pale; acid; 1012; faint trace of albumin. Sediment, slight; epithelial cells; few small hyaline casts.

5th. Patient, feeling perfectly well, leaves the hospital against advice.

On May 17th the patient returned to the hospital, having had a chill two days before, after which she had taken quinine. The blood was free from parasites and no further chills occurred; the treatment was continued.

Physical examination was negative.

The *urine* was examined frequently during the next two weeks; it was always perfectly normal. The urea, estimated on one occasion, amounted to 0.028 per c.cm. On June 2, 1897, the patient was discharged, well.

CASE XIX. *Malarial fever; æstivo-autumnal infection; acute hemorrhagic nephritis; recovery* (?).—No. 20,421. J. P., male, aged thirty-eight years, was admitted August 25, 1897. Family history good; no history of infectious diseases. The patient had chills as a child and again last year. For four weeks he has suffered from chills and fever off and on; for three weeks there have been swelling of the legs and abdomen, drowsiness, ischuria, dyspnœa.

Physical examination. Pallor; general œdema and ascites; double hydrothorax; no cardiac hypertrophy; pulse tension rather high; spleen not palpable.

Blood. Æstivo-autumnal parasites; hyaline amœboid bodies; crescentic forms.

Urine. Deep amber; slightly turbid; acid; 1020; albumin abundant. Sediment, flocculent; hyaline casts, with epithelium, pus, and blood adherent; free blood and pus.

There were febrile paroxysms on the 25th and 26th, the temperature remaining normal after the beginning of quinine—0.325 (gr. v) three times a day—on the 27th. The œdema and ascites rapidly disappeared.

The *urine* was reduced in quantity on the 26th and 27th (880 and 560 c.c.). From this time on there was polyuria, amounting to 2200 c.c. on September 1st. The albumin steadily diminished in quantity. On September 2d the urine was of normal color; acid; 1015; no albumin; microscopically, a few hyaline casts are still to be found in the sediment. The patient left the hospital, against advice, feeling perfectly well.

CASE XX.—*Vide* page 363.

CASE XXI.—*Vide* page 364.

CASE XXII. *Malarial fever; type ?; acute nephritis; recovery*(?).—L. S., male, colored, aged forty-three years, visited the out-patient department on March 27, 1895. Family history negative; measles and whooping-cough as a child; chills and fever in spring of 1894. For three weeks he has complained of cough and expectoration; for three days he has had chills and swelling of the legs; frequent micturition.

Physical examination. Pallor; œdema of the legs; harsh breathing, with fine crackling râles at the apex of the right lung.

Blood. Malarial parasites found; type not mentioned.

"*Urine.* Albuminous ring quite marked with HNO_3."

Treatment. Quinine.

April 10, 1895, feels better in every way.

CASE XXIII. *Malarial fever; tertian infection; acute nephritis; result* (?).—K. W., female, aged seventeen years, visited the out-patient department on July 31, 1896. Family history negative; has had measles, otherwise no serious illness. The patient has had chills previously. For ten days there have been daily paroxysms.

Physical examination. Tongue coated; nasal and labial herpes; spleen palpable.

Blood. Partially grown tertian parasites.

August 14th. Chills have disappeared, but a week ago noticed œdema of the feet; scantiness of urine.

The *urine* contained large amount of albumin; hyaline and granular casts; numerous bladder and vaginal epithelial cells.

Treatment. Milk diet, rest in bed, quinine.

The patient did not report again.

CASE XXIV. *Malarial fever; tertian infection; acute nephritis; recovery* (?).—F. G., female, aged twenty-three years, visited the dispensary August 17, 1896. Family history negative; has had no serious illness. The patient has never had malarial fever; for a day or so, very severe headache.

Physical examination. Marked pallor; moderate œdema of the legs.

Urine. Decided trace of albumin; epithelial cells; leucocytes; numerous coarsely and finely granular casts.

August 22d. Returned to-day, complaining of having had three tertian chills, the last on Sunday; severe headache.

Blood. Tertian parasites; half-grown forms.

Under quinine the patient made a perfect recovery. Seen again March 17, 1897, feeling perfectly well. No further examinations of the urine were recorded.

CASE XXV. *Malarial fever; æstivo-autumnal infection; acute hemorrhagic nephritis; result* (?).—J. S., aged twenty-one years, visited the out-patient department September 28, 1897. Family history negative; measles as a child. The patient had never suffered from malaria previously. Two weeks ago two chills; since then swelling of the face and legs came on, and he has complained of bad taste in the mouth.

Physical examination. General œdema; no cardiac hypertrophy; spleen palpable.

Blood. Æstivo-autumnal organisms; nemerous crescents.

Urine. Smoky, bloody; contains a large quantity of albumin.

Treatment. Advised to enter hospital. The patient did not return.

CASE XXVI. *Malarial fever; æstivo-autumnal infection; acute nephritis; arterio-sclerosis.*—J. M., aged forty years, visited the out-patient department October 20, 1896. Family history negative; always strong and well. For four weeks and a half the patient has had chills off and on, his first attack; headache, vertigo, and swelling of the feet for a week.

Physical examination. Pallor; œdema of the legs; apex impulse under the sixth rib in mammillary line; sounds clear; radial arteries thickened.

Blood. Æstivo-autumnal parasites; numerous crescentic bodies.

" *Urine* has marked amount of albumin."

The patient refused to enter the hospital and failed to report at the dispensary again.

DISCUSSION.

DR. F. FORCHHEIMER: I wish to corroborate in a general way the statement as to the frequency of kidney troubles in the æstivo-autumnal form of malaria. We have been having quite a number of cases of æstivo-autumnal malaria during the last fall and winter, and I can say that very few of them have run their course without the production of some complications of the kidney.

My experience differs somewhat from that of Dr. Thayer, in that the majority of the cases I have seen were found in children, and the younger the child the more extensive the complications and the longer they lasted.

What I arose especially to speak of, though, was a peculiar form of nephritis that I have seen in the last fifteen years, producing a deposit of pigment in the urine in the course of malaria. The first patient I remember was an adult, in whom my attention was called to the condition of the urine. It had separated into two layers, the upper being very clear and the lower almost black. I found it contained a large quantity of albumin, casts, blood-corpuscles, and large masses of pigment, which, under the microscope, was brown or, where thinner, slightly reddish. This was in the days before we knew of the plasmodium, and since that time I have taken more pains to study these cases, and have succeeded in finding this peculiar form of pigment in cases in which the tertian parasite was present, as well as in those cases produced by the æstivo-autumnal parasite. As good fortune would have it, I succeeded in obtaining a specimen of urine from a little patient of sixteen months with well-marked æstivo-autumnal malaria, and with symptoms almost resembling the comatose form. In this patient albuminuria was present, a large quantity of albumin being found in the urine, which also showed, microscopically, casts and blood-corpuscles. About two weeks after the disease had begun these peculiar pigment bodies began to show themselves in the urine. As I said before, they are characterized by their peculiar appearance, and can be recognized macroscopically. They are very heavy and sink rapidly to the bottom of the vessel. I have no suggestion as to their nature. I have never been able to collect a sufficient quantity to make a chemical analysis.

The idea occurs that this is melanin, but these granules are very large, and it would be almost inexplicable to think of melanin forming such large masses. I have noticed that after a chill these pigment bodies are largely increased in number, and so the view that they may come from melanin cannot be positively rejected. Again, it is possible that this pigment may be due to some other modification of hæmoglobin, but all hypotheses must be kept in abeyance until spectroscopic and chemical examinations can be made.

Dr. W. Osler: I think our figures, though high, are not so high as they would have been had we in the early years of the hospital work paid greater attention to this subject. I was a little sceptical at first as to the frequency of malarial nephritis.

As to the point Dr. Thayer referred to, the importance of albuminuria in the diagnosis between yellow fever and malaria, I think he did not lay sufficient stress upon the fact that in yellow fever the albuminuria occurs very, very early—within the first twenty-four hours—to be of importance in the diagnosis.

It is very interesting to know that we have had no single case of hæmoglobinuria that could be attributed in any way to quinine. We have as yet to see a case of quinine hæmaturia or hæmoglobinuria, which is rather remarkable, considering how frequent the condition is supposed to be in the South.

Dr. A. JACOBI: I would like to ask whether the findings in Baltimore are the same in different years, as these figures extend over a number of years. Are there seasons that have been exempt? I ask the question because there are a number of observers, like Heidenhayn, who have stated that they have found no albuminuria in successive seasons, and then all at once there was a year in which it was frequently encountered. Rosenstein saw many on the Baltic Sea, few in Friesland. I know in my wards lately there have been sixteen or eighteen cases of malaria, and not one had albuminuria, and yet in former years I found it. We in New York are not well situated for studies of that kind, because it is only in exceptional years, such as the present, that we see much malaria.

DR. I. E. ATKINSON: I have for many years been convinced that malaria is an important factor in kidney changes, and that a certain percentage of nephritic cases would be found almost constantly. It may of course vary very much, but I am positive it would always be larger than we think. There is difficulty in deciding whether we have actual nephritis sometimes, for, though we have albuminuria and anasarca, it is difficult to determine whether the anasarca is due to nephritis or whether it is purely the cachectic anasarca that is so frequently present in a high degree.

There is another point, though, that it would be well to have attention paid to, and it is this: whether in localities where mortality statistics are kept, nephritis is in any degree more prevalent in malarial countries than in countries where malaria does not prevail. Of course, such statistics would be more or less unsatisfactory, but it is only by the comparison of statistics for a long series of years that it can be determined. In Maryland we have no vital statistics that are at all reliable outside of Baltimore, but the last Legislature passed a law that compels the keeping of such statistics, and possibly in a few years we can help to throw some light upon that question.

DR. JAMES TYSON: I think that what Dr. Jacobi said for New York is true for Philadelphia. I have naturally been on the lookout for nephritis in connection with malaria, and I have met it very rarely. The cases we have originating with us in Philadelphia are of the mild types, the severe cases being found mostly in seamen who come from southern ports. In the case of chronic nephritis, I have for years been looking out for cases to ascribe to malaria, and I think two, three, or four would probably cover all that my note-book contains in which there is any reason for suspecting a connection between the two.

DR. H. M. FUSSELL: I can confirm this for Philadelphia, especially in the northeastern part of the city, where malaria is more frequent than elsewhere. In none of our cases at the St. Mary's Hospital last year was there the condition described by Dr. Thayer, and in very few was there any albuminuria

DR. THAYER: That our figures do not show a larger proportion of cases of nephritis among children may be explained by the small number of children

treated in our wards. I have received, however, to-day a letter from Dr. W. P. Northrup, describing an interesting case of this nature. Dr. Northrup has kindly permitted me to mention the case. The patient was a child, aged two years, the daughter of rich parents living in good hygienic surroundings in New York City. The child suffered from irregular temperature, with daily rise and fall, the urine showing blood, abundant albumin, and numerous hyaline and granular casts. Malarial parasites were found in the blood, and complete recovery occurred in a few days under quinine. The case occurred in April, 1898.

I have never seen anything like the interesting pigment bodies which Dr. Forchheimer has demonstrated in the urine. The pigment masses are very large, and quite unlike the ordinary malarial pigment seen in the circulating blood.

With regard to the question of quinine hæmoglobinuria, it is an interesting fact that its occurrence seems to be limited to special regions. One cannot, I think, fail to be impressed by the surprising statement of Bastianelli,[1] that not a single instance has ever been reported from the Roman Campania, a region in which malaria has probably been more carefully and intelligently studied than in any other part of the world.

The variation in the frequency of albuminuria and nephritis in different epidemics, as referred to by Dr. Jacobi, is very strongly brought out by our observations. The majority of all cases of malarial fever in 1894, 1895, and 1896 showed albuminuria, while during 1897 it was present in only about 26 per cent. of the cases. Sixteen out of twenty-six instances of nephritis occurred during the summer of 1896.

I have not been able to find in literature much that is positive concerning the greater frequency of chronic nephritis in malarial regions, though there are some observations which would lead one to believe that this is the case. Rowland, for instance, has called attention to the relative frequency of the disease in British Guiana, a very malarious dsstrict.

[1] Ann. di Med. Navale. ii., Rome, 1896.

THE RENAL FORM OF ENTERIC FEVER.

By J. C. WILSON, M.D.,
OF PHILADELPHIA.

THE prominence of certain symptoms in cases of enteric fever, the evidences of intense implication of special organs and occasional modifications in the course of the attack, have given rise to various attempts to arrange the cases in categories and to describe special forms of the disease.

We find in systematic writings upon the subject descriptions, more or less complete, of the following forms of enteric fever: 1, The mild, or typhus levissimus; 2, the latent or ambulatory form—walking typhoid; 3, the abortive form; 4, afebrile enteric fever; 5, the enteric fever of childhood—so-called infantile remittent fever; 6, enteric fever in the aged; 7, hemorrhagic typhoid, the last being a rare form, commonly fatal, characterized by hemorrhages into the skin and from mucous surfaces, and corresponding to the hemorrhagic forms of variola, measles, and other infections. These categories are similar to the groupings of cases made by common consent in the descriptions of other acute diseases, and unquestionably serve a useful purpose. When, however, we observe a disposition to set up other lines of division and to group the cases upon a different system of classification, we are impressed with the unsatisfactory results of nosological refinements. To describe bilious and sudoral forms and to speak of ataxic and adynamic types is neither scientific nor convenient; nor for the student does it simplify the subject to constitute distinct varieties, such as pleural, pulmonary, cerebro-spinal, and renal. Nevertheless, aberrant forms of which these terms are descriptive are encountered. They are too rare to constitute varieties of the disease; too common to be disregarded in systematic descriptions.

Some years ago a woman, aged about forty years, was admitted to

my service in the hospital of the Jefferson College, who presented the general symptoms of enteric fever with the physical signs of a croupous pneumonia. The illness began suddenly with chill and very high temperature. The case terminated fatally. Upon autopsy the abdominal lesions of enteric fever were found, and Eberth's bacilli were recovered from the pulmonary exudate.

The wife of a physician was taken suddenly ill with intense headache, vomiting, and painful rigidity of the muscles of the back of the neck. The heart's action was feeble and irregular. There was active febrile movement of remittent type. At the end of a week the cerebrospinal symptoms abruptly ceased, rose-spots appeared, the spleen became enlarged, and the case ran the course of an uncomplicated enteric fever.

A Russian boy, aged four years, was admitted to the Pennsylvania Hospital on the fourth day of an illness, attended with pain in the limbs and swelling and tenderness of the belly. Upon admission there was slight, painful rigidity of the muscles of the back of the neck, together with spasmodic contractions of the muscles of the arms and hands. Except dilatation, there were no pupillary symptoms, no strabismus, no trismus. There was no disease of the ears. A few hours after admission the patient's temperature suddenly fell from 102° to 93° F. It rapidly rose again. The child was fretful, and preferred to lie upon his side with his limbs strongly flexed. He cried out with pain upon being moved. Ankle-clonus was present, and the knee-jerks were increased. A small amount of albumin, with hyaline and granular casts, appeared in the urine. There were one or two herpetic vesicles upon the lips, and a few pustules upon the occipital region and upon the trunk; the tongue was moist, thickly coated with a white, pasty fur; it was red at the tip and edges. Upon the third day after admission a group of typical rose-spots appeared upon the abdomen and chest, and the spleen was made out to be enlarged. About this time there was rapid amelioration of the nervous symptoms; the reflex phenomena subsided; pain on movement disappeared, and the case presented the symptoms of a typical enteric fever of moderate severity in childhood. Treatment, systematic cold bathing. Convalescence retarded by furunculosis.

The following case, recently seen in consultation with Drs. Byers and Hobson, is an example of the renal form of enteric fever—nephrotyphoid:

A lad, nineteen years old, salesman, who had never had enteric fever and whose previous health had been excellent, began about December 10, 1897, to complain of weakness and loss of appetite. A few days later he had head-

ache and was feverish in the evening. It was noticed that he was unusually pale. On December 24th he was obliged to abandon his work and remain in bed. About this time headache became severe.

From this time on there was continued fever, the temperature ranging from 99.3° F. as a single minimum in the morning, to 105° F. as a maximum in the evening, until the fifty-fourth day, when it became normal, and remained so. During the greater part of this period the temperature fluctuated between 102° and 104° F. From the time the patient was obliged to remain in bed until January 8th, namely, a period of fifteen days, the symptoms were those of an acute nephritis. The urine varied in specific gravity from 1010 to 1030, and showed large amounts of albumin, together with erythrocytes, leucocytes, epithelial cells, and granular casts. The breath was urinous, the skin hot and dry, and there were delirium and occasional vomiting, with a slight puffiness under the eyes, but upon the most careful examination no œdema elsewhere. An examination of the eye-grounds by Dr. Hansell showed engorgement of the venous circulation, but no retinitis or any signs of past trouble. The amount of urine was about twenty-five fluidounces in twenty-four hours.

The patient did not improve under treatment directed to this condition, including calomel and saline purging, hot-air baths, and cut cups in the lumbar region, although under this treatment the quantity of urine voided was increased to sixty ounces in twenty-four hours. He became greatly emaciated and weak. On January 8th the following note was made: General condition much improved, but the patient continues to be extremely weak. The temperature now ranges between 99° and 101° F. The amount of urine voided amounts to eighty or ninety ounces in each twenty-four hours. The albumin is greatly diminished, casts have almost entirely disappeared, one only now and then being found in the field. A few blood-corpuscles are occasionally seen. For the first time the patient on this date passed blood in the stools.

Small amounts of blood continued to be present in the discharges from the bowels for eight days. Prior to this time the case had been carefully studied from the stand-point of a possible enteric fever. Abdominal symptoms were not, however, present, rose-spots could not be found, nor enlargement of the spleen made out. An examination of the blood now, however, gave a positive reaction to the Widal test. A liquid diet consisting chiefly of milk had been administered from the beginning of the attack.

On January 26th it was noted that the urine is free from albumin but still contains a few erythrocytes and leucocytes. The temperature has fallen to 99.3° F. From this point the temperature began steadily to rise to the former level, the patient became delirious, albumin reappeared, together with granular casts, leucocytes, and erythrocytes. On February 2d there were diarrhœa and tympany, but no spots. On the 3d a rather copious crop of the rose-spots of enteric fever appeared. From this time on until February 19th the progress of the case was that of enteric fever. Fresh crops of spots appeared, increase in the area of splenic dulness could be made out, the ten-

dency to diarrhœa persisted. Albumin, casts, and blood-corpuscles disappeared from the urine. Finally, the patient developed the intense hunger so characteristic of the early convalescence of enteric fever. At the time of writing, April 15th, the urine continues to be normal.

In this case the extended febrile movement covers an obscure primary attack in which the kidneys manifestly bore the brunt of the infection, and a relapse occurring without interval—so-called intercurrent relapse—in which the ordinary symptom-complex of enteric fever is present with renewed evidences of inflammation of the kidney. Such cases are extremely rare. Their recognition is, however, of great importance.

Aside from the general theoretical importance of a correct diagnosis, we must consider here certain practical points. First, while the kidneys may, as in the foregoing instance, for a time bear the brunt of the attack, the ordinary intestinal lesions may also be present, and in this particular case the occurrence of hemorrhage was, without doubt, the evidence of a deep ulceration attended with the danger of perforation. There are then practically two clinical dangers in these cases which render the recognition of their essential nature necessary to the welfare of the patient: first, the danger of the administration of an improper diet, and, second, that of the improper use of purgatives. To mistake a case of enteric fever of the renal form for one of acute nephritis eliminates to a great extent, on the part of a prudent practitioner, the first of these dangers, since the regulation of the nourishment and a diet consisting largely of milk or dilute porridges would enter into the scheme of management, but there are those who are not altogether strict in regard to the diet of their cases of acute nephritis, by whom fruits, certain vegetables, or other solid foods might be permitted.

The danger from an error in diagnosis is altogether greater with reference to the use of purgatives, since the administration of calomel in full doses, and salines, enters very largely into accepted plans of treatment for acute nephritis. The diagnosis is, however, as difficult as it is important, and must remain in many cases an impossible one until the disease has made some progress.

Of even greater importance is the etiological danger which attends an error in diagnosis. From the stand-point of preventive medicine the failure to recognize a case of enteric fever is attended with risks

to the community far greater than any danger that may affect the interests of the individual patient. The final destruction of the infecting principle in the stools and urine by efficient disinfection means the arrest of the spread of the disease upon the spot so far as any particular case goes. To neglect this procedure amounts practically to a crime against the State. The differential diagnosis between enteric fever and any other disease with which it may be confounded involves, from this point of view, enormous responsibility.

The following case well illustrates the difficulty of diagnosis:

I saw recently, in consultation with a medical friend, at about the end of the second week of her illness, an unmarried woman thirty-six years of age, who had been taken sick gradually with headache, great weakness, fever, tendency to diarrhœa, and other evidences of enteric fever. The spleen was enlarged. There were no rose-spots. The tongue was red at the edges and tip and heavily coated with a yellowish-white fur. In the course of a routine examination the evidences of an acute nephritis had been discovered in the urine. There was slight præ-tibial œdema. The temperature ranged between 102° and 104° F. The general appearance of the case was that of enteric fever of mild type. At my suggestion the agglutinating power of the blood-serum upon Eberth's bacilli was tested (Widal test). About seven weeks later I was informed by the physician in charge that the convalescence of the patient was practically assured. In addition he wrote as follows: "After you saw the case her temperature pursued a zigzag course, gradually declining and becoming normal about the twenty-second day after the nurse arrived," about the twenty-ninth day of the attack. "There was some mild delirium, and after some days the tongue became dry and glazed. The albumin disappeared as the fever subsided, but after some days there developed a phlebitis of the left leg, after which albumin was again temporarily present in the urine. No rose-spots were discovered. The Widal test was negative. While willing to admit that the Scotch verdict of 'not proven' is applicable to this case, I still feel that it was one of typhoid infection."

In this case a repetition of the Widal test at a later period was unfortunately not made. The patient ultimately entirely recovered, with permanent disappearance of albumin.

The agglutination test is of the utmost importance in finally settling the question of diagnosis in doubtful cases. In the group of cases under consideration, however, its value is greatly impaired by the fact that in a certain proportion of the cases the power of arresting the motility of the typhoid bacilli and causing agglutination does not show itself until the disease has made considerable progress—not ear-

lier in some cases than the end of the second or some period in the course of the third week.

It is of practical importance, then, to treat all doubtful cases in which, for the time being, the differential diagnosis between subacute or acute nephritis and enteric fever cannot be made as possible cases of enteric fever. Certainly this method of management is imperative as regards the regulation of the diet and the disinfection of the stools and urine—matters which involve no risk in any case and which recommend themselves for acceptance in doubtful cases in view of the fact that in the majority of instances in which this particular differential diagnosis is in question the sickness will ultimately prove to be enteric fever.

THE DIFFUSE INFILTRATING FORM OF SECONDARY MELANO-SARCOMA OF THE LIVER AND ITS ASSOCIATION WITH ASCITES.

By LUDVIG HEKTOEN, M.D.,

AND

JAMES B. HERRICK, M.D.,

OF CHICAGO.

Secondary sarcoma of the liver may occur in the form of circumscribed masses and nodules, as a diffuse infiltration of the whole liver, or in the form of a mixture of both varieties. The reports in the literature show that so far secondary melano-sarcoma is the only histological variety of sarcoma that possesses the remarkable faculty of growing diffusely throughout the liver, so that in time the organ becomes almost entirely replaced by tumor tissue. The text-books of pathological anatomy (Ziegler, Birch-Hirschfeld, Kaufmann, and others) contain good descriptions of the striking marmorated appearances of the liver, the seat of diffuse, infiltrating secondary melano-sarcoma, and pathologists are agreed that secondary sarcoma of the liver as well as elsewhere is of metastatic and hæmatogenous origin. In the diffusely infiltrating variety single cells immigrate more or less continuously into the intralobular capillaries of the liver, where they multiply within the vessels and cause a gradual disappearance of the columns of liver-cells by a process of pressure atrophy. These migrating cells may pass through the capillaries of the lungs and probably also of the intestines, because in the vast majority of the cases it concerns primary melano-sarcomas of the eye or its immediate vicinity. As a general rule, secondary tumors develop elsewhere in the body also, especially in the lungs, but the liver seems to furnish the best conditions for the lodgement and the further growth of the tumor-cells.

As already stated, the majority of the secondary melano-sarcomas

of the liver are due to metastasis of a primary tumor in or near the eye. A good account of the literature concerning the nature and location of these occular and orbital melano-sarcomas is given by L. P. Hamburger[1] in a recent report of two cases of secondary melano-sarcoma of the liver following sarcoma of the eye. In one case post-mortem showed a nodular metastasis in the liver which weighed 8.3 k. In connection with this report Abel makes some valuable remarks concerning the chemical composition of the pigment produced by these tumors.

The two following cases are interesting as typical examples of the diffuse, infiltrating form of secondary melano-sarcoma of the liver in their clinical as well as anatomical features; they have an additional and greater value, however, because they illustrate the development of ascites from portal obstruction, due to intracapillary proliferation of tumor tissue in the liver. As far as can be learned from the literature the development of ascites on this basis has not been noted in connection with secondary sarcoma of the liver. In Musser's[2] case there developed ascites two weeks before death; but this is apparently attributed to a concomitant "dense fibrous hyperplasia" in the liver, which weighed 8.5 k. (17½ pounds), and was the seat of a "round-celled sarcoma with melanosis." The patient, a man, forty-two years old, died from the hepatic symptoms two and one-half years after the removal of the left eye for melano-sarcoma.

CASE I.[3] *Diffuse infiltrating melano-sarcoma of the liver, secondary to melano-sarcoma of the choroid of the right eye; ascites due to occlusion of the capillaries of the liver and consecutive thrombosis of the intrahepatic branches of the portal vein.*—Man, aged fifty years, manufacturer, of dissolute habits, came under the care of Professor Holmes at the Presbyterian Hospital, September 17, 1895, on account of loss of vision in the right eye, which dated back about three years. Professor Holmes diagnosed the condition of the right eye, which was protruding and nodular, to be due to a melano-sarcoma of the choroid. Physical examination was otherwise practically negative. On November 15th some ascites had developed, and on the 25th of this month the ascites had become pronounced; there was jaundice, and the urine contained bile pigments. The patient was passed into the care of Dr. J. A. Robison, and thanks are due to both Professor Holmes and Dr. Robison for

[1] Bulletin of the Johns Hopkins Hospital, 1898, ix.
[2] Proceedings of the Philadelphia Pathological Society. New series, vol. i. 2.
[3] L. Hektoen. Transactions Chicago Pathological Society, 1897, ii. p. 138.

their permission to make this very brief extract from the clinical history of the case.

The patient died December 7, 1895, apparently from exhaustion. The post-mortem examination was made one hour after death. The anatomical diagnosis reads: Melano-sarcoma of the right eye and the orbit; atrophy of the right optic nerve; metastatic tumors in the lungs, pleuræ, and left kidney; diffusely infiltrating metastatic melano-sarcoma of the liver; chronic congestion of the spleen; thrombosis of the intrahepatic branches of the portal vein; ascites; general bile pigmentation; chronic nephritis; chronic (left) orchitis; general arterio-sclerosis.

The body is much emaciated; the skin and visible mucous membranes yellow; the right eye protruding, the eyeball nodular; the orbit is filled with a hard mass; the cornea turbid.

The abdominal cavity contains a large quantity of yellowish fluid; the peritoneal layers are smooth. The pleural and pericardial cavities are empty.

The heart weighs 450 grammes; endocardium normal.

The lungs are œdematous and contain a few small solid nodules that are grayish and in places almost black on the cut surface. Similar smaller masses are found here and there in the pleuræ. The larynx, trachea, and peri-bronchial glands are normal.

The spleen is firm, very dark red in color, contains much blood, and weighs 450 grammes.

The kidneys weigh 350 grammes; the surface is irregular, the cortex thin, the consistence firm. In the left kidney is a small, subscapular tumor nodule. The left testicle is firm, fibrous.

The liver is very much increased in size, the left lobe being almost as large as the right; it weighs 4100 grammes. The external surface is rather finely nodular, mottled bluish and gray in color; many small pinhead sized and a little larger gray tumor masses are seen on the surface. In consistence the liver is very dense and firm, like sole-leather or hard rubber. The cut surface is also irregularly nodular or granular, the predominating or ground color being bluish black with small gray districts here and there, so that the general appearance of the surface is best described as granite-like or variegated, like marble. The large vessels in Glisson's capsule and the branches of the portal vein are filled with rather softly coagulated blood.

The gastro-intestinal tract is normal, but the mucous membrane is slaty in color; the pancreas is normal.

The aorta and the splenic artery show a rough and irregular intima.

The skull and the brain are normal, the vessels at the base being sclerotic.

The interior of the right eye is partly filled with a firm tumor that seems to spring from the choroid, is quite black on the cut surface, and largely replaces the vitreous humor; at the entrance of the optic nerve the tumor extends for a short distance backward in the substance of the nerve, and at the corneo-scleral junction of the internal aspect of the globe the tumor tissue perforates all the coats of the eye and spreads out into a walnut-sized retro-

bulbar tumor mass, which is grayish-white in color, with only here and there blackish or brownish dots and areas. The right optic nerve is smaller than its fellow and gray in color.

Blood-serum tubes inoculated from the heart's blood and the ascitic fluid remained sterile.

The microscopical examination of the tumor of the eye and the pulmonary and renal nodules show the structure of a typical melano-sarcoma; the pigmentation is most uniform in the eye; in the other places the majority of the cells are not pigmented, but chromatophores occur in all.

The liver shows but remarkably little true liver structure; it consists almost entirely of tumor tissue, which is, speaking broadly, very much pigmented; typical slender, branching cells filled with brownish pigments predominating. Often the amount of intracellular pigment is so marked that the nucleus is hard to see. Groups of and single non-pigmented cells also occur. Wherever the hepatic structure persists the capillaries are filled with tumor-cells, often to an excessive degree, producing a marked compression of the adjacent columns of liver-cells, whose gradual disappearance from atrophy can be traced from the early to the final stages, when but narrow, almost imperceptible bands of protoplasm remain, to be succeeded by coalescence of the intracapillary tumor growths. As the result of this form of growth the tumor has an indistinct alveolated appearance.[1] Careful scrutiny failed to show any histological appearances that would point to removal of the liver-cells by means of phagocytic action of the cells of the tumor. In the larger vessels are often found single cells as well as masses of tumor-cells. Remnants of, as well as intact, biliary ducts are found principally in a somewhat thickened Glisson's capsule, which is the seat of a small degree of round-cell infiltration. Otherwise there has been no connective-tissue increase in the liver. In some of the larger vessels are hyaline thrombic masses, the exact nature of which is doubtful, because the pieces examined were hardened in Müller's fluid.[2] In some places the tissue in what must be parts of Glisson's capsule presents an appearance as though it were œdematous.

CASE II. *Melano-sarcoma of the eye following trauma; extirpation and recurrence; secondary infiltrating sarcoma of the liver, with ascites.*—Herman K., native of Germany, a resident of Cook County, Illinois, for eighteen years, by occupation a farmer, entered Dr. Herrick's ward in the Cook County Hospital, September 22, 1897. Of his family history he knew little; there was no hereditary taint so far as he was aware. He himself had been temperate as regards the use of liquors, had escaped venereal infections, and had been singularly free from preceding serious illness. He was the more surprised, therefore, to find that during the past year, and particularly during the last six months, he had been losing in flesh and strength. His chief complaint was

[1] The alveolar structure is not nearly so well marked as in the second case, presumably because the infiltration has been more uniform, the embolism and the intracapillary growth occurring at the same time and with the same degree of rapidity throughout the organ.

[2] Chicago Pathological Transactions, 1897, ii. p. 273.

of his weakness and of a feeling of fulness and hardness in the epigastrium that had annoyed him for about four months. For one week there had been considerable distention of the abdomen. He complained of no pain whatever; had a good appetite; never vomited; bowels were regular.

Inquiry as to the circumstances leading to the loss of his right eye elicited the information that three years before he had been kicked over the right eye by a horse, the eye, or the parts in the immediate vicinity, becoming greatly swollen. This swelling soon subsided, and the eye gave no further trouble until two years after, when it became swollen, "red like a beefsteak," and the sight failed. The eye was removed at the Illinois Charitable Eye and Ear Infirmary one year prior to his admission to the County Hospital.

Status Præsens. There is marked emaciation; the skin is dry, scurfy, and of a muddy look; there is no icterus. The movements are evidently painless, though he is plainly very weak. The breath is fœtid, the teeth decaying.

The left eye is normal; the right eye lacks the globe. Beneath the drooping lid a small, hard nodule can be felt, and the muco-purulent discharge comes from a reddish mass of granulations, and is often blood-tinged.

The lungs are clear. Over the lower right chest the dulness, continuous with that of the liver, rises in front and behind one inch higher than normal. The heart's action is rapid and snappy; its apex-impulse is in the fourth interspace close to the nipple, as though displaced by the enlarged liver. The arteries are tortuous and have slightly thickened walls.

The abdomen is distended, and the signs of free fluid can be made out. The liver is plainly palpable in the mammillary line, its border being a hand's breadth below the costal arch. Dulness in front is to the fourth rib. The surface of the liver feels firm and coarsely granular; it is not tender. In the epigastrium there is a distinct bulging forward. The edge is somewhat irregular or scalloped, and is very hard. No nodules are anywhere distinctly made out. The liver descends freely with inspiration. The firm, hard mass of the liver, the patient tells us, has been noticed by him for about four months. No changes can be made out in the other abdominal organs. The stomach is not enlarged; its contents were not examined. The rectum and genitalia are negative; the umbilicus is prominent; the inguinal glands are perhaps slightly enlarged, as are the axillary. There is œdema of the ankles and legs, and slight œdema of the abdominal wall.

Scattered over the surface of the chest and abdomen are several hard, painless, freely-movable nodules, apparently in the subcutaneous tissue. The largest, the size of a large lima bean, is just inside the vertebral border of the left scapula. The color of some of the nodules as seen through the skin is slightly black. One of these nodules in the abdominal wall was excised for purposes of diagnosis. This showed small, round- and spindled-celled structure, with considerable fibrillated stroma; in occasional areas the cells contained small granules of brownish-yellow pigment, which also occurred free between the cells. Diagnosis, melano-sarcoma.

The urine contained neither sugar, albumin, nor casts. When fresh it was

clear, of a reddish-yellow color, and acid. On standing for several hours it became of a darker hue and still remained acid. With strong sulphuric acid and with nitric acid the color changed to a dark brown. On the addition of a small amount of a strong solution of ferric chloride a grayish precipitate was produced, which dissolved in an excess of the reagent. With bromine-water a yellowish precipitate that gradually darkened was formed. These tests were regarded as evidence of the presence of melanogen in the urine, a common finding in cases of melanotic growth. In every instance the test was controlled by similar tests with other urines.

The diagnosis was therefore made of melanotic sarcoma of the eye, with metastases in the liver and subcutaneous tissue, and with recurrence of the growth at the original site. This diagnosis was further confirmed when an examination of the records at the Eye and Ear Infirmary showed that the eye had been removed for melanotic sarcoma. Careful examination was made for evidences of involvement by metastasis of the lung, pleura, and pericardium; but neither by symptoms nor by physical sign of friction, dulness, or altered respiratory or circulatory tone, was there any revelation of the existence of nodules in these organs. The dulness from the small amount of fluid in the right pleura was believed to be due to the enlarged liver.

The question naturally arose as to the condition of the liver and the cause of the ascites; whether we had to deal with a sarcomatosis of this organ or with sarcoma in a cirrhotic liver. Notwithstanding the fact that the statement is made by some authors that in sarcoma of the liver ascites does not occur, the fluid in the abdomen was regarded as probably due to the growth in the liver; and this, from the absence of distinct nodules in a liver of this enormous proportion, was looked upon as probably of the diffuse infiltrating variety. The solution of the clinical problem was rendered much easier by the recollection of the specimen of diffuse infiltrating sarcoma of the liver associated with ascites, shown by one of us at the Chicago Pathological Society a short time before.[1]

That the fluid in the abdominal cavity was a transudate seemed probable from the fact that on October 9th a pint of clear serous fluid was withdrawn by puncture, and its specific gravity was but 1007. In the fresh and stained specimens from this fluid no pigment-containing cells were found. Nor were any cells resembling sarcoma

[1] Hektoen. Transactions Chicago Pathological Society, 1897, ii. p. 138.

cells, or large cells with the atypical mitoses described by Rieder,[1] Dock,[2] and Wharthin[3] found. The peritoneum was presumably free from tumors and the fluid due to portal obstruction.

ANATOMICAL DIAGNOSIS: *Absence of right eye: pigmented tumor in right orbit growing into optic nerve; pigmented and pigment-free tumors in the skin, the muscles, the lymph nodes, the pleura, the lungs, and the myocardium; diffuse tumor infiltration of the liver; ascites; right hydrothorax; left adhesive pleuritis, with slaty induration of left apex; œdema of the legs; ecchymosis in the floor of the fourth ventricle; sclerosis of the coronary arteries and of the aorta; chronic nephritis.—Abstract of post-mortem protocol:* The body is wasted; the right eye is absent, and the orbit is filled with a nodular mass, which is blackish on the cut surface. In the skin of the anterior surface of the chest are three or four movable, split-pea sized, slightly pigmented nodules; in the muscle to the left of the dorsal part of the spine is an oval tumor, 2 x 4 cm., with areas of blue pigmentation.

There are small pigmented masses in the anterior mediastinum; considerable clear fluid in the right pleural cavity; the left is obliterated by adhesions. In the pulmonary and diaphragmatic pleura are innumerable pedunculated and sessile tumor masses of varying size; there are tumors in the lung-substance and in the peribronchial glands.

In the epicardium are many tumor nodules, the largest being over the anterior wall of the right ventricle near the coronary sulcus; the nodules are grayish or whitish in color. Attached to a papillary muscle in the left ventricle is a minute, pedunculated black mass. The coronary arteries and the aorta are somewhat sclerotic. The heart weighs 300 grammes and the endocardium is smooth. The abdominal cavity contains several pints of clear yellowish fluid; the peritoneum is smooth and shining. There are no thrombi in the portal vein or its large branches. The mucous membrane of the intestines is normal; that of the stomach rather slaty in color. In the omentum and mesentery are many small nodules.

The liver weighs 5000 grammes. It is the seat of a uniform enlargement that seems to involve the right lobe more that the left; the surface is mottled-gray and bluish-gray or black, and is quite smooth for the most part, but over the left lobe and along the lower margin of the right it is rough and even nodular, due to grayish or bluish projections; the consistence is very firm. On the cut surface the left half of the liver has a more bluish color, the right half a more yellowish-gray, the line of junction being in some parts very sharp and recognizable on the external surface; but mottled areas of variegated appearance like marble also occur, as well as distinct nodules of varying sizes. Any traces of normal liver-substance are not to be seen. The gall-bladder contains a small amount of bile. The pancreas, the spleen, the

[1] Rieder. Deut. Arch. f. klin. Med., Bd. lix.
[2] Dock. American Journal of the Medical Sciences, June, 1897, vol. cxiii.
[3] Wharthin. Medical News, October 16, 1897.

genito-urinary organs, and the adrenals are free from tumors; the surface of the kidneys is finely granular; the consistence increased. In the floor of the fourth ventricle are small hemorrhages; the tumor in the orbit extends in the optic nerve to the commissure, filling the nerve with a bluish-black mass.

THE MICROSCOPICAL EXAMINATION. Pieces from all the tumor masses were examined after the usual technical preparations.

The pigmented as well as pigment-free masses outside of the liver may be dismissed with the general statement that in the main they are made up of rather closely-packed, small, spindle- and round-cells that run in interlacing bands of varying thickness, which, cut across, give the tissue an alveolar appearance; here and there occur characteristic chromatophorous cells in small groups or scattered about singly.

A number of pieces were studied from different parts of the liver, in order to obtain a clear notion of the relation of the tumor-cells to the structural elements of the organ. It may be said at once that almost the whole liver has become substituted with tumor, whose further expansive growth has been limited and so directed by the original framework of the liver that the resulting mass, at time of death weighing 5000 grammes, still preserves the outline of the liver. It concerns, therefore, a diffuse, infiltrating sarcoma of the liver.

Here and there in the uniform infiltration occur, as seen with the naked eye, distinct nodules. In these rather avascular areas the structure is indistinctly alveolar, the spaces being closely packed with rather small, mostly pigment-free, sarcomatous cells. A few small, multinucleated cells are seen. The pigmented cells are mostly long-drawn out, branching, even star-shaped, and also round; the pigment is yellowish or deep-brown, mostly granular, sometimes scaly; at times covering all parts of the cell densely, at other times it is gathered along the borders of the cystoplasm or at the ends of the processes. When the processes are cut off free-pigment heaps are simulated. The pigment-cells seem to prefer the outskirts of the spaces and to lie in the more distinct fibrous bands. Their shape and the arrangement of pigment granules are best seen in unstained preparations.

In the flat infiltration the alveolar arrangement of the cells is very prominent. The spaces are of various size, round, oval, more rarely oblong; the walls of the spaces are sometimes very indistinct, sometimes made up of a distinct layer of fibrous tissue, with narrow, elongated nuclei; again of endothelioid cells, and finally remnants of bands of liver-cells may be met with. The cells in the alveoli are mostly pigment-free, oval, round, or polygonal, with rather small bodies and deeply stained nuclei; a few chromatophorous cells are frequently observed, and in some districts they predominate. Now there are extensive areas corresponding to this general description without any further trace of liver-structure and but few bloodvessels; occasional bands of hyaline connective tissue may be seen with vessels, and perhaps two or three rows of low columnar cells without any arrangement to form any distinct lumen; distinct but empty bile-ducts also occur.

The early stages of this replacement process are clearly made out on studying parts where some distinct liver-tissue still persists. In the first place, it is notable that all, or almost all, the capillaries encountered contain tumor-cells among the blood-corpuscles or free in the empty lumen. The majority of these cells are chromatophorous, and the long-branched, star-shaped form of this cell is seen most typically among the blood-cells. The majority of the persistent capillaries and vessels are unduly congested. From this beginning there can be readily traced a progressive intracapillary growth of melano-sarcoma, which crowds out the blood, distends the capillaries to the utmost, and produces a pressure-atrophy of the liver-cells. In the earlier stages the rows of liver-cells are still distinct, but the cell-bodies soon lose their outlines and become amalgamated into protoplasmic bands that stain deeply with eosin and are thickly set with nuclei; the bands become thinner, the nuclei smaller and more closely crowded together, until the resultant alveoli of tumor-cells come into contact with one another. From the histological appearances it seems that a purely mechanical pressure atrophy of the liver-structure precedes its often complete replacement with tumor-tissue.

While the early capillary tumor-cell emboli seem to be principally chromatophorous, the more advanced intracapillary proliferations may in some cases produce pigment-free cells in predominating numbers, hence this may account for some of the extensive non-pigmented areas which, as seen on the surface of the liver, are most sharply demarcated from the pigmented districts. As already remarked, the process is everywhere so far advanced that nothing can be said as to just in what part of the lobule the free cells become first arrested, nor can any exact details be made out with respect to the hepatic veins or smaller bile-ducts.

In a number of pigment-free, or but slightly pigmented, cells are karyomitotic figures.

It is, finally, worthy of note that any proliferation and induration of the fibrous tissue has not occurred to the slightest degree.

CASE III. *Melano-sarcoma of the right eyelid; extirpation; secondary sarcoma of the liver, presumably infiltrating, and of the peritoneum, with ascites; no autopsy.*—Jos. P., aged fifty-four years, German, laborer, was admitted to Dr. Herrick's ward in the Cook County Hospital. Family and personal history negative. In May, 1897, a dark-colored, easily bleeding nodule of two-years' standing was removed from the right upper eyelid, together with one-half of the lid, by Dr. D. A. K. Steele. On February 28, 1898, the patient felt so weak that he gave up work, which was loading coke. He had lost in weight, was short of breath, and was distressed by the increasing size of the abdomen.

Examination, March 22, 1898, in Cook County Hospital, showed emaciation and weakness. One-half of the right upper eyelid was left, and showed nothing abnormal. Both eyes were the seat of a conjunctivitis with a mucopurulent discharge. No growth could be demonstrated in either eye; vision was good. Several dark-colored nodules intimately connected with the skin

were scattered over the body, the smallest about the size of a pin-head, the largest, situated in the scalp over the right parietal region, as large as a hickory-nut. The lungs and heart were negative. There were signs of fluid in the right pleural cavity; by aspiration, clear, light-yellowish serous fluid. Cells containing fat and brownish pigment found in the sediment. There was free fluid in the abdominal cavity; 6500 c.c. were withdrawn. It was clear, yellowish; specific gravity 1018.

The sediment obtained by centrifugalizing the fluid was fixed by alcohol and ether and stained in various ways. The cells varied in size from that of a small lymphocyte up to those three or four times as large. They were round or oval, with large rounded nuclei centrally or marginally situated. Many large and medium-sized cells with two or even three or four nuclei were found. No karyokinetic figures were seen. Occasionally a dumb-bell-shaped nucleus was noticed, looking as though about to separate into two. In many cells there were reddish-brown pigment granules or quite large masses. Free pigment granules were scarce. The protoplasm in most of the cells took the stain faintly.

After the withdrawal of the fluid the liver could be palpated, its edge extending nearly to the umbilicus. The enlargement was chiefly in the right lobe. The surface and edge were hard, not nodular. In the right half of the epigastrium the enlargement caused a visible bulging. The spleen was not palpable. No masses or nodules could be felt in the abdomen. The lower extremities were not œdematous.

The red blood-cells were of normal size, shape, and color; they numbered 4,500,000 per cubic millimetre; white cells 9680, with slight polymorphonuclear increase. No abnormal pigment was seen in the blood in fresh or stained specimens. Hæmoglobin 80 per cent. (Fleischl).

The urine was scanty; fifteen ounces for twenty-four hours. It was acid; specific gravity 1030; no albumin, no sugar, no casts. Tests for melanogen with sulphuric acid, bromide-water, and ferric chloride, all positive and controlled by tests with known normal urine.

The diagnosis seemed clear of a pigmented growth involving the liver, skin, pleura, and peritoneum, and presumably secondary to the primary growth removed in May, 1897, from the eyelid, which growth had existed for two years. To confirm the diagnosis and to determine more accurately the nature of the tumor, one of the nodules from the chest was removed and examined microscopically. This showed a fibrillated stroma with an alveolar arrangement packed with small round- and spindle-cells. Reddish-brown pigment granules and masses were seen here and there, having a tendency to be arranged in the fibrillary tissue and parallel with the fibres, but being found also in and among the round- and spindle-cells. Diagnosed as a melanotic sarcoma. It was further learned from Dr. Steele's clinic that the diagnosis of the tumor of the lid at the time of operation had been melanotic sarcoma. Unfortunately the patient refused to stay at the hospital and left at the end of a few days.

In general the structure of the tumors agrees closely with that laid down by Hugo Ribbert,[1] as peculiar for the melano-sarcoma, or melanoma, as he would prefer to call the tumor in question, of the eye. The essential structure of the various growths is identical. The presence of the characteristic pigment cells in the majority of the areas, although in greatly varying numbers and degree of pigmentation, demonstrates clearly enough that it concerns metastatic tumors secondary to melano-sarcoma of, in these cases, the right eye. Of the secondary growths especial attention is called to the diffuse infiltrations in the liver. The first two cases, and probably the third, are typical instances of the diffuse infiltrating variety of secondary sarcoma of the liver.

The histological examination points to a remarkably extensive and uniformly diffuse capillary embolism of tumor-cells. In one case these cells passed almost unhindered through the pulmonary capillary network, as only a few tumor-nodules were present in the lungs. In the second case cells were arrested in the lungs, the pleura, the myocardium, the pericardium, the skin and subcutaneous tissue, and an implantation nodule developed on the endocardium of the left ventricle; in other words, a more extensive generalization took place; but in both cases the capillaries of the liver afforded the best conditions for the arrest and further growth and proliferation of the cells in the blood. Apparently the cells reached the liver through the hepatic artery rather than through the portal vein, because there were no metastases in the capillaries drained by the vein; but in view of the uncertain and accidental manner in which secondary tumors may arise, only conjectures in regard to this point are permissible. In the liver, however, the favorable condition for cell-growth resulted in the development of a diffuse intracapillary growth, which replaces the liver-tissues proper while it largely retains the normal external conformation of the organ. In both cases this process is everywhere so far advanced that it cannot be said in what part of the lobule the cells are first arrested.

As indicated, the capillary tumor-cell emboli seen at first are oftenest chromatophorous; as these cells proliferate large numbers of pigment-free cells are produced, and there result in this manner large districts,

[1] "Ueber das Melanosarkom." Ziegler's Beiträge, 1897, xxi.

and in one case more distinct nodules, also, of non-pigmented tumor-growth. It is a well-known fact that the cells of the metastatic melano-sarcomas have a tendency to lose their original physiological property of producing pigment. Ribbert looks upon the round, non-pigmented cells in such foci as incompletely developed. An exact explanation of the origin of extensive pigmented and non-pigmented areas with well-marked, definite margins cannot be advanced; it is easy to suggest that this feature, which was well marked in the second case, may depend upon accidental distribution of pigmented and pigment-free cell emboli.

There is absolutely nothing in the histological appearances, which are quite plain, that would warrant the inference advanced by some, that the melanotic cells exercise a proliferative or "infectious" stimulus upon the cells with which they come in contact, leading to an active participation of pre-existing elements in the growth of the secondary tumor-tissue; on the contrary, it is quite plain that the metastatic process that has led to the replacement of the liver with tumor-tissue is one of continuous intracapillary tumor-growth, resulting in, as far as can be specified from the microscopical appearances, a mechanical pressure atrophy of the intervening liver-substance associated with compression and occlusion of the structures in Glisson's capsule. As the capillaries and smaller vessels become packed with tumor-cells the portal circulation is hindered, ascites develops, and in one case thrombosis of the intrahepatic branch of the portal vein was induced. The development of ascites upon this basis—*i. e.*, occlusion of the hepatic capillaries by sarcomatous cells, to which attention was drawn in the report of the first case[1]—is exceedingly interesting, and does not seem to have been mentioned in the descriptions of this remarkable form of secondary sarcoma of the liver.

These cases deserve notice from a clinical as well as anatomical point of view.

In Case II. there was a clear history of local trauma two years before the removal of the eye. This is so common in cases of melano-sarcoma as to attract attention in all series of cases. Lawford and Collins[2] found local injury several months, or even three years,

[1] Transactions of the Chicago Pathological Society, 1897, vol. ii.

[2] Lawford and Collins. "Sarcoma of the Uveal Tract, with Notes of 103 Cases." Royal London Ophthalmic Hospital Reports, 1891, p. 104.

before the removal of the eye for melano-sarcoma in 6.79 per cent. of cases. P. Wagner,[1] in nineteen cases of melano-sarcoma, reports a history of trauma in five.

The frequency with which the liver is secondarily affected is commented upon by all writers. In our three cases the involvement of the liver was at the time of observation the predominating feature.

In Case III. the primary tumor was apparently in the eyelid—an unusual locality.

In the matter of diagnosis we would emphasize the importance of careful inquiry as to the nature of existing eye-troubles and of causes for extirpation of eyes seen to be missing. Further painstaking search for cutaneous and subcutaneous nodules should be made. Many of these are extremely minute and to be detected only by diligent examination, their existence not being known to their possessor. The extirpation of one of these nodules for microscopical examination is a simple matter, but of great aid in diagnosis.

As to the configuration, size, and consistency of the liver, it may be said that in the diffuse infiltrating form of sarcoma the liver seems to preserve nearly the normal shape, though, with its measurements, greatly increased. It is hard and, if the abdominal wall be thin enough, may be felt to be slightly roughened or coarsely granular. In the mixed form the surface may be uneven from nodules, and these may be hard or soft, fluctuating, and containing fluid (Litten's case).

While other causes for melanuria than melanotic neoplasms are not unknown—*e. g.*, malaria—the presence of melanin or melanogen in the urine adds strong confirmatory evidence of the existence of a melanotic growth, in the liver for example, if that be enlarged. Melanogen is a colorless chromogen that first becomes black by oxidation, and is then called melanin (Litten). A single negative examination of the urine should not be regarded as excluding a pigmented tumor, for in some cases neither melanin nor its chromogen has been present, and in others the melanuria has been periodical. We would emphasize the value of control tests with normal urine as greatly limiting the possibility of error. The question of the nature of these pigments in the urine is fully discussed by Litten.[2]

[1] P. Wagner. "19 Fälle von Melanosarkom." Münch. med. Woch., August 16, 1887.

[2] Litten. "Ueber einen Fall von Melanosarkom der Leber." Deut. med. Woch., January 17, 1889.

The occurrence of ascites should not, as some authors state, argue against sarcoma of the liver. Its clinical association without peritoneal origin is demonstrated by Cases I. and II., and the cause seems not obscure when we consider the pathological condition present, the plugging of the hepatic capillaries by sarcoma cells. In our second case the small omental nodules did not seem a sufficient explanation of the fluid, which further possessed the characteristics of a transudate—specific gravity 1007. In our first case no cause for the ascites save the hepatic growth was discovered. In Litten's case, which was nodular, to be sure, there is no mention of involvement of the peritoneum, yet there was a moderate amount of ascitic fluid in the lower part of the abdomen. In our third case we believe, from the character of the fluid, that the peritoneum itself was the site of multiple metastasis. That other causes for ascites than plugging of the vessels by sarcomatous masses may exist is, of course, true. A portal thrombosis, a sarcomatosis of the peritoneum, and accompanying nephritis or hepatic cirrhosis (as in Musser's case) may give rise to ascites. But the fact should not be overlooked that ascites may occur, and often does occur, in uncomplicated sarcoma of the liver, at least in the secondary, infiltrating, melanotic form.

We would add a word as to the value of the examination of the fluid aspirated from the serous cavities in cases of suspected involvement of the lining membranes in melano-sarcomatosis. In Case II. no pigmented cells were found, nor any cells of unusual size or shape or with nuclei showing atypical mitoses. The fluid was, further, of low specific gravity (1007), and resembled, therefore, in every particular a transudate. In Case III., however, where we believe the peritoneum was involved in the new growth, not only was the fluid of higher specific gravity (1018), as in exudates, but the cells were much more numerous, and many of these were large. Many cells contained reddish-brown pigment granules as well as fat-drops.

CASE OF CHRONIC INFECTIVE ENDOCARDITIS, WITH STREPTOCOCCI FOUND IN THE BLOOD BEFORE DEATH,

TREATED WITH ANTISTREPTOCOCCUS SERUM, AND EXPERIMENTS ON THE EFFECTS OF INJECTIONS OF SERUM AND OF ANTITOXINS UPON THE KIDNEYS.

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THE patient, an anæmic and delicate-looking gentleman, aged thirty-six years, called first at my office on September 3, 1897. He stated that he once had weighed 187 pounds, at which time he was a high liver and took stimulants freely. These he gave up, and then enjoyed good health until three years ago, when he had a prolonged attack of dyspepsia, coming on very suddenly, from which he lost heavily in weight. He gradually improved until fifteen months ago, when his digestive troubles all returned, and for them he then came to me.

He described his symptoms as a constant distress from flatulence in his stomach and bowels, which also caused much disturbance of the heart. He had no pain in his stomach, and his gastric symptoms were neither increased nor relieved by taking food. In addition, he also detailed a train of nervous symptoms, consisting of attacks of severe periodical neuralgias in the forehead and in the left hypochondrium, with paræsthesiæ in his legs, a feeling of great weakness in the lower part of the spine, and darting pains in the legs, arms, and hands. On examination, his pupil reflexes were normal; he swayed a good deal when his eyes were shut, his eyelids then being very tremulous; his tongue was very tremulous, and both knee-jerks were much exaggerated. He had a constant hacking cough, which, however, he said that he had had for years without any expectoration.

On examination his lungs were found normal. Heart: apex-beat within nipple line, impulse good, and careful percussion showed no enlargement. A slight systolic thrill was palpable at the left edge of the sternum and fourth interspace. On auscultation there was a harsh systolic murmur, most intense at mid-sternum opposite fourth interspace. This murmur was heard over the whole precordium, in the axilla and down the back, and was so loud

that it drowned the normal first and second sounds, which could be distinguished only to the left of the apex and in the right carotid; the murmur transmitted with the greatest intensity to the left third costal cartilage. I told the patient that he had a very noisy murmur accompanying the action of his heart, but that I believed it had been there all his life. He and his wife both smiled at this statement, and he replied that a number of physicians had told him that he had serious heart trouble, and that he should be very careful on that account; but that his parents told him he was born a blue baby, and that he continued blue till he was three years old, after which he had no further difficulty with his heart, and that he had been something of an athlete in his youth, and, as a society man, he had been very fond of dancing.

A third set of symptoms was then detailed of a different character. Three months before, on June 4th, he was taken with a fever, which lasted six weeks, characterized by an access of chilliness regularly at 4 P.M. This fever so reduced him that he was removed to the country; but, instead of improving there, his afternoon chilliness developed into pronounced rigors, followed by high temperatures and sweats, with rapid emaciation. During the febrile attacks his cough was incessant, which led one physician to pronounce him far gone in consumption. Meantime in the city more than one medical attendant diagnosed his attacks as malarial, and accordingly he was freely dosed with quinine, Warburg's tincture, arsenic, etc., but without benefit. Finally, according to him, his chills and fever left him, but his dyspepsia and neuralgic troubles grew worse.

I at first prescribed for his gastro-intestinal and neuralgic troubles and for his general nutrition, apparently with benefit for six weeks, his calls being made at my office, and while there in morning hours his temperature was never above normal. On one occasion, two weeks after beginning treatment, I received word from him of his suffering from such severe attacks of nocturnal pain in the left hypochondrium that he had no relief but from free hypodermics of morphine. I sent him directions to try drachm-doses of the fluid extract of ergot, a drug which I have found specific in many cases of periodical neuralgia, and he reported that it relieved him at once, so that he was able to sleep for the first time in six nights. He then continued with varying dyspeptic and nervous symptoms, though on the whole claiming that he was much better than before for four weeks, until, as he reported, a return of his afternoon chilliness and night-sweats, I supplied him with a thermometer to take his temperature at such times.

The next day his temperature at 3 P.M. was 98.6° and at 8 P.M. 102°, followed by night-sweats. The following day his temperature was below normal in the morning, but reached 103° in the evening. His blood was now examined for plasmodium malariæ, and on the first occasion some suspicious pigment granules in the corpuscles led to the hope that his periodical fever might be malarial, a surmise rendered more probable from the above-mentioned relief of his nocturnal pains by ergot. He was accordingly put

upon doses of quinine and arsenic. The arsenic soon had to be given up on account of gastric irritability, and then the quinine was intermitted to give greater chance to discover plasmodia, if present. But a second examination, eight days after the first, showed no plasmodia, and likewise a third a week after that. Meantime his progressive emaciation and other general symptoms had led to repeated search for evidence of tuberculosis, on account of the frequency of this infection in subjects of congenital heart-disease, as well as from his chronic cough, though this was never accompanied with expectoration. But no indications of pulmonary or of abdominal tuberculosis were discoverable, and repeated examinations of his urine failed to show any tubercle bacilli. A blood-count at this time showed red corpuscles, 4,500,000; hæmoglobin, 60 per cent., with moderate leucocytosis.

By December 8th the persistence of his periodical fever, with very irregular range from day to day, varying from 99° to 104°, forced the conclusion that his was a case of infective endocarditis. To what an extent this diagnosis was based wholly on the clinical feature of intermittent pyrexia may be inferred from the facts that not only was there no evidence of either tuberculosis or of leukæmia, but also that no indications of embolism, either external or internal, could be detected. Though constantly looked for during many weeks, he never showed spots or ecchymoses anywhere, no enlargement of liver or spleen, and only transient tenderness to pressure in various parts of the body. A curious fact was that from December 1st to December 28th his temperature-curve showed a tendency to a maximum rise every seven days. He now began to have severe rigors, lasting from half an hour to an hour, which his wife said were exactly like those which he had during the summer. His urine after such rigors would become quite albuminous, with some blood-corpuscles. On December 27th he was seen by Dr. E. G. Janeway in consultation, who confirmed the diagnosis of infective endocarditis as the only condition to account for his fever. On December 30th blood was drawn from his left median vein by Dr. James Ewing, assistant pathologist of the Roosevelt Hospital, with careful precautions to prevent contamination from the skin. On January 1st Dr. Ewing reported that numerous streptococci were found in the blood, which, by cultivation in the Pathological Laboratory of the College of Physicians and Surgeons, on blood-serum, agar, and gelatin, proved without doubt to be streptococci pyogenes.

On January 1, 2, and 3, 1898, the patient had from two to three chills a day, the highest temperature being 105°, and he would become delirious each night. As his condition now seemed desperate, I decided to have recourse, as a last resort, to antistreptococcus serum, particularly as I have read accounts in British medical journals of three recoveries from presumed infective endocarditis by the use of streptococcus antitoxin—one by Dr. Harrington, of Sainsbury, by Dr. Margaret Pearce, of Brighton, and by Dr. J. A. Washbourn, of Guy's Hospital. The antistreptococcus serum was kindly supplied to me (made fresh, so as not to be over a week old) by Dr. W. H. Park, of the laboratory of the New York Board of Health, who took

much interest in the case, and who recommended that serum in preference to Marmorek's antistreptococcus serum, which Dr. Park states that he has found to become inert after some weeks' keeping.

The patient received in all nine injections, given hypodermatically by my assistant, Dr. Robert Coleman Kemp, in five days, the total amount thus administered being 155 c.c., with the following history: On January 3d the first injection was made of 15 c.c. at 12 M. His temperature then was 97.8°. At 5 P.M. he had a chill; at 8 P.M. temperature was 104.2°; at 8.45 P.M. he had a second injection of 10 c.c. From 12 to 3 o'clock that night he was very delirious. January 4th he had an injection of 10 c.c. at 10 A.M.; his temperature rose to 100° at 4 P.M.; at 7 P.M. he had a chill, lasting three-fourths of an hour; temperature, 104.4°; at 9 P.M. he had an injection of 15 c.c.; January 5th, at 12 M., 15 c.c., and at 8 P.M. 15 c.c. Half an hour afterward a chill came on, which lasted an hour and a quarter; temperature, 104.2°. He had frequent hiccough, and was delirious all night. His urine now began to diminish in quantity and became quite bloody. January 6th, at 12 M., injection of 25 c.c., much hiccough following, and at 8 P.M. he had retention, so that he was catheterized, and 10 ounces of bloody urine were drawn off, which was the only amount secreted in eleven hours.

At this time it was proposed to try enemata of normal saline to relieve the total suppression which was impending. Three ounces were administered at 8 P.M. Half an hour later 25 c.c. of antistreptococcus serum were injected; at 8.40 and at 9.15 P.M. normal saline was again given by enema, making 9 ounces in all. The effect of the saline seemed immediate, for 40 ounces of urine, much less bloody, were passed in five hours after it was begun. But he had a chill at 11.15 P.M., when his temperature rose to 105.4°, and he lay in a stupor all night. The next morning, January 7th, he was quite rational and ate a good breakfast, and by 10 A.M. he had passed 58 ounces of urine since commencing the saline enemas of 9 ounces, as before mentioned, fourteen hours before. He took his last hypodermic of serum of 25 c.c. at 9 A.M.

The subsequent history of the case after suspending the administration of the serum hypodermatically was: Saline enema of ℥iij at 2 P.M. and at 7.30 P.M., then with 30 c.c. of antistreptococcus serum by enema. At 10 P.M. he had a chill, which was stopped immediately by an enema of ℥iij of saline. An hour later he had another chill, which seemed also to be arrested by ℥iij of saline; but at 12 P.M., with a temperature of 104.2°, the chill returned, and was not arrested by a further saline enema, but lasted one and one-fourth hours. Quantity of urine in 12 hours, 36 ounces. January 8th. Saline enemas, ℥iij, kept up every three hours; two enemas of 35 c.c. and 40 c.c. of antistreptecoccus serum were given; urine passed in twenty-four hours, 32 ounces. His chill came on at 12 P.M.; temperature, 105°. He now lay in a stupor all day, with pinhole contraction of the pupils, until he was roused to consciousness, when they would widely dilate. On January 9th, in the morning, he was quite rational, 50 c.c. of serum were given by enema, and

the saline injections kept up. He had no rise of temperature that night, though he had slight rigors. He remained in a stupor again all night, and the urine again diminished to ℥viij in twenty-four hours. January 10th he had retention, and had to be catheterized; urine in twenty-four hours, 9 ounces. Hot saline irrigation with Kemp's rectal irrigator, using 2 gallons at a time, was now used, with immediate effect in stopping the rigor for half an hour; then it returned, but was stopped again by the irrigation, and the temperature did not rise afterward above normal. Antistreptococcus enemata omitted. January 11th. Hot irrigations every three hours. The patient had no nocturnal chill nor febrile temperature; urine in twenty-four hours, 11 ounces; patient comatose all day. January 12th. Irrigations continued. He passed 1½ ounces of urine once after irrigation; otherwise, by catheterization, only 1½ ounces were obtained. Died quietly at 6.45 P.M.

To our extreme regret, no autopsy was allowed by the patient's friends.

From a purely clinical point of view, this case presents some points of interest. The presence of a loud cardiac murmur, due to congenital malformation of the heart, altogether prevented any auscultatory evidence of the presence of the infective lesion which was the primary cause of the patient's death. But it does not necessarily follow that such a lesion would have been discoverable had there been no such congenital derangement. A number of years ago a boy, aged fifteen years, was brought to me by his parents for extreme anæmia, accompanied by irregular chills and fever, which he had been suffering from for five months, and it was noted that after each chill he had rheumatoid swellings of his knuckles with ecchymotic spots on the backs of his hands. I examined his heart repeatedly, but could discover nothing wrong there. The late Drs. Alonzo Clark and Austin Flint also saw him with me in consultation, and each of them reported his heart as free from any lesion. I remember well how both of these distinguished consultants were perplexed to account for his chills and for their accompanying ecchymosis. Infective endocarditis was not then recognized as a distinct malady, but afterward both endocarditis and pericarditis suddenly developed, and the boy died hemiplegic.

Some years ago a woman was admitted to my wards in Bellevue Hospital with severe periodical chills and fever, coming on regularly at 9 P.M. In her, also, I could detect no cardiac murmur, but I diagnosed infective endocarditis, on account of the gravity of her general symptoms, though she had no surface indications of emboli. At the autopsy a small deep ulceration was found in the wall of the ventricle just underneath the mitral valve.

This present case also renders it extremely probable that many deaths which formerly were ascribed to chronic malarial disease were really due to infective endocarditis. Hardly a clinical characteristic of chronic ague was absent from his history. He had periods of deceptive improvement, with apparent cessation of his febrile attacks, followed by a recurrence of them with all the regularity of a well-established quotidian, and even with some indications of a seventh day exacerbation. Moreover, his neuralgic attacks were often periodical, and one, particularly complained of above the left eye, was very similar to so-called brow-ague. It would seem, therefore, as if a streptococcus infection may be characterized by a cyclical development of the streptococcus itself in the blood, as we know to be the case with the plasmodium malariæ, and which has been adduced as an explanation of the periodicity of the paroxysms of ague. It is remarkable, however, that streptococci were so certainly demonstrated in the blood of this patient, with the natural inference of their presence in the circulation for months, and yet without any signs of localized inflammation or of purulent deposits anywhere in the body, even the sites of our hypodermatic injections never showing inflammatory reaction, though the entire absence of such internally could not be affirmed without an autopsy.

Though this patient had previously shown considerable albuminuria with some blood-corpuscles after his rigors, particularly during the week preceding the first injection of antistreptococcus serum, yet so pronounced became the signs of hemorrhagic nephritis within thirty-six hours from the date of his first serum injection, and then these continued with such severity, along with increased rigors and fever, that the question arose whether the serum did not itself aggravate the derangement of the kidneys. This question of deranging the kidneys has been raised frequently about all injections of antitoxins, and it seemed to me, therefore, very desirable to institute some experimental researches to determine the effects upon the kidneys of antistreptococcus serum in particular, and then of other forms of serum injections. Accordingly, the following experiments and observations have been conducted by my assistant, Dr. Robert Coleman Kemp, under my supervision, in the Laboratory of Physiology of the New York College of Physicians and Surgeons, the free use of whose great facilities we owe to the courtesy of Prof. John G. Curtis.

The animals used were dogs; the total number in this set of experiments was fourteen. Tracheotomy was first performed and a rubber tube was attached to the tracheotomy tube. This was to allow of artificial respiration if necessary, and for the ready administration of ether, besides allowing the respiratory tracings to be taken. The right carotid was dissected out and then connected with Ludwig's mercurial manometer and kymograph, sodium carbonate solution having been introduced previously in a glass canula to prevent blood clotting. The right kidney was thoroughly freed from perirenal fat and cleared down to its pedicle, and then inclosed in the oncometer of Mr. J. T. Hoyt, Electrician and Mechanician in the Physiological Laboratory of the College of Physicians and Surgeons, and in which, in distinction from Roy's oncometer, water is used instead of oil. The oncometer was connected with Hürthle's drum and kymograph, and a column of air was inclosed in the tube connecting the oncometer with the drum, whose oscillations could be readily perceived in a piece of glass tubing inserted in the rubber tubing. By this means we soon perceived that Hürthle's small drum presented too great resistance to register our oncometric tracings well, and this was afterward obviated by using the larger drum of Marcy. To the connecting tube a lateral stop-cock was attached, so that the tension of the water in the oncometer or of the air column could be easily regulated.

As the success of the observations depended so much upon the accuracy of the oncometric tracings, special efforts were made to improve the transmissions of the waves in the air and water columns by the drum to the registering lever, until finally a drum specially made by Mr. Hoyt enabled us to exchange Marcy's tambour for one which gave such excellent tracings that we show the accompanying illustrations of a comparison between the two. In the first illustration the kidney was that of an undersized dog, and was so small for the oncometer that the tracings with Marcy's tambour are barely large enough to recognize the characteristic lines, while as soon as Hoyt's was substituted, the excursion of the registering lever was ample for all purposes. In the second illustration, with the kidney of a large dog, the tracings are larger and fuller in detail than any oncometric registrations which we are acquainted with. The use of water instead of oil, as in Roy's oncometer, also made Hoyt's instrument much more convenient to adopt, and to insure a speedy beginning of trace-taking;

a great recommendation in such experiments, as Dr. Kemp was able thereby to perform the operation of incising for the kidney and adjusting it in the box and start the tracing on the kymograph in ten and a half minutes, thus insuring a minimum of disturbance in the renal circulation.

The next step was to insert a glass tube in the left ureter, the drops of urine from which were arranged to strike a registering lever by means of another drum on the Hürthle kymograph, on a line above the oncometric tracing, so as to measure the rate of urinary secretion. The left ureter was thus tapped, as affording a more trustworthy indication of the state of urinary secretion than the right kidney, which was necessarily more or less disturbed by the manipulation requisite for inclosing it in the oncometer. The urine collected was also examined microscopically and analyzed.

For recording respiratory tracings, a glass Y was inserted through a cork and this placed in the soft rubber tube which had been joined to the tracheotomy tube. While respiration was carried on through the large branch of the Y, the smaller branch was attached by a soft tube to a third drum and lever on the kymograph, and the respirations thus recorded. In some animals the respiratory tracings could not be secured because the diversion to the drum of even a small amount of air interfered too much with their breathing.

Certain difficulties, inseparable from all such experiments, were encountered, such as that in some dogs their kidneys were too large for the oncometer, and in others too small, while functional differences of circulation between different animals, or varying susceptibility to anæsthetics, etc., had to be taken into consideration. We were, however, early led to note that the administration of ether caused wider variations in the oncometric tracings than any other one factor, and, what was more significant, that these took place without much correspondence with the simultaneous carotid tracings, thus indicating a specific local action on the renal circulation. This often occurred and to such an extent that it rendered the effects of serum injections in a number of dogs too uncertain for safe deductions, thus causing us much loss of time. Ultimately, however, we were enabled to distinguish these results of ether so as to eliminate them in the interpretation of the effects of serum injections. Our mode of procedure was to give morphine in doses of a grain to a grain and a half, and then

FIG. 1.

Effects of ether.

to use the ether along with it as sparingly as was consistent with the requisite state of anæsthesia.

As the subject of the effect of ether inhalation upon the circulation of the kidneys is one of wide interest, we give here illustrations of oncometric tracings in the same dogs when ether was first administered, then suspended, and then again freely given. This first effect is seen to be a rise, followed by a more decided fall in the blood-pressure in the kidney, when the oncometric curve is seen nearly to disappear, to reappear again when the animal is coming out of the influence of the ether, and lastly, when free administration is resorted to, an extreme fall of blood-pressure and complete disappearance of the oncometric curves. That these changes are due to a specific effect of ether upon the renal circulation is shown by the simultaneous carotid tracings not being appreciably changed.

Experiments with Antistreptococcus Serum.

Experiment 1. Normal dog, eight kilos in weight, was injected with 5 c.c. antistreptococcus serum at 3.32 P.M., again at 3.34 and at 3.40, and then at 3 58, or 20 c.c. of serum. In about three minutes after the last injection the kidney pressure began to fall. The urine rapidly diminished in quantity as registered by the drops on the kymograph. The amount now collected was found to be albuminous. At 4.16 5 c.c. more were injected, and at 4.27 a descent occurred in the glass tube in the ureter of a reddish fluid, well defined from the line of urine. As before described, this was not the kidney inclosed in the oncometer, so that this could not be ascribed to the manipulation of the kidney, and, to establish its source, a careful examination of the ureter up to the pelvis of the kidney was made, and it was thus shown that the bloody fluid was coming from no other source than the kidney itself. On microscopical examination this fluid proved to contain both blood-corpuscles and dissolved hæmoglobin. Afterward the kidney itself, on being removed, appeared macroscopically intensely congested.

Experiment 2. Normal dog, weighing 11.460 kilos, was injected with antistreptococcus serum at 3.46 P.M., also at 3.48 and 3.50 and 3.55, in all with 20 c.c. in the course of nine minutes. As in the previous experiment, after 20 c.c. had been administered—in about one and a half minutes after the last injection—the kidney pressure began to fall, nearly reaching, in about two and a half minutes, the registering line of seconds. The tracings remained close to this seconds line, and at times touching it, doing so at 4.05, when all oncometric waves wholly disappeared, showing complete stasis in the kidney. At this time 5 c.c. more of antistreptococcus serum were injected. A few seconds later a faint trace appeared above the seconds line, to disappear and reappear again, and then for about one minute and a

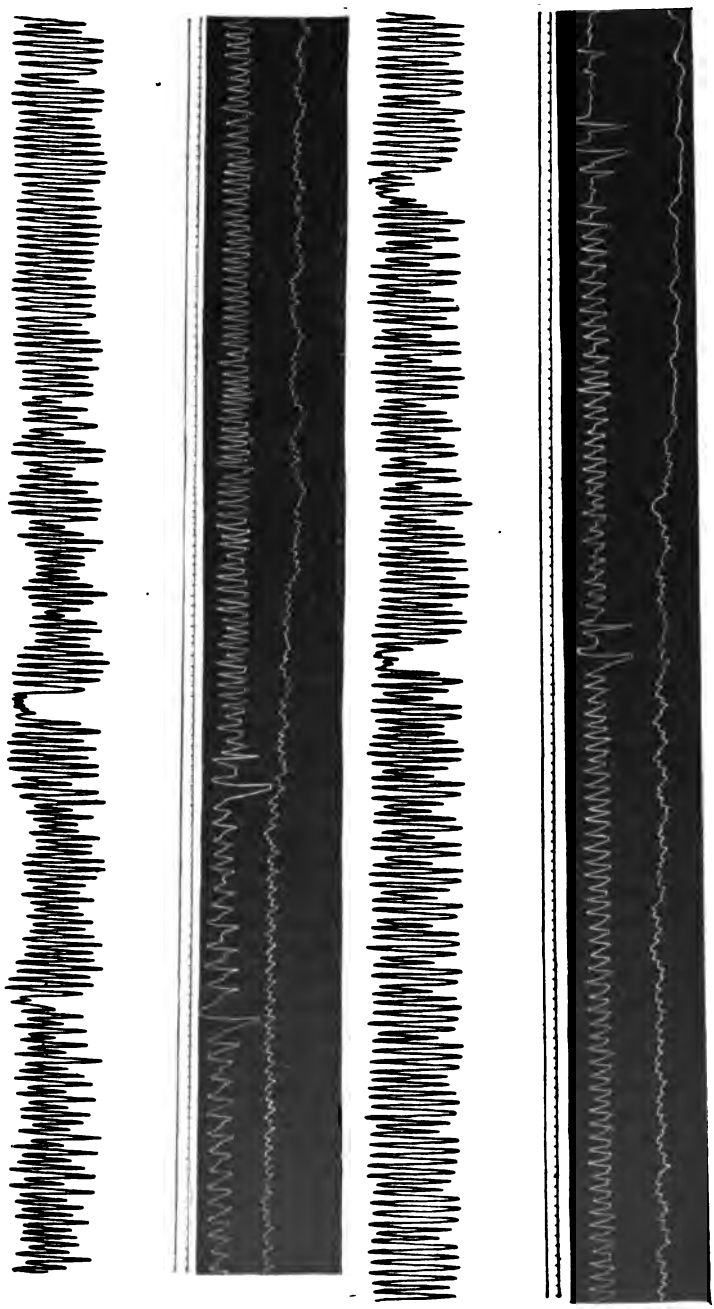

FIG. 2.

Effect of antistreptococcus serum.

half there were alternate rises and falls above the seconds line, but so minute that they were barely perceptible. The tracings then gradually became more distinct, and at 4.08 were clearly marked, but still remaining close to the seconds line. On this account the seconds line was at this time shifted down half an inch to clear the line of the renal tracings. These latter still remained at the same low level as before, though now more visible. At 4.10 5 c.c., and at 4.12 5 more were injected; also at 4.14 and at 4.15, when the animal gave several deep gasps which momentarily affected the tracings. The renal line then dropped lower than ever, and the tracings wholly disappeared. During this whole experiment no ether was administered. After the last injection was administered, amounting in all to 45 c.c. of antistreptococcus serum, the urine, which had been rapidly diminishing in rate of secretion, became bloody, and on examination showed the same admixture of blood-corpuscles and dissolved hæmoglobin as in the previous experiment.

Comparing now the kidney tracings with the general blood-pressure registered simultaneously in the carotid tracings, we start with a pressure of 135 mm. at the beginning of the experiment. When the serum injections begin to affect the kidney there is an irregular fall of the general blood-pressure of from 5 to 8 mm., though soon rising to normal again. When the renal tracings touched the seconds line at 4.05, just previous to which the pulse-trace stood at 135 mm. there was a sudden fall of 30 mm., but in fifteen seconds it was up to 135 mm. again, though the kidney pressure remained very low. The general blood-pressure remained with irregular variations of not more than 10 mm., but after several more serum injections, at 4.15 it again rose to 135 mm., and then dropped to 107 mm., and then rose again irregularly to 120 mm., and soon again to 135 mm. Meanwhile there was absolute stasis in the renal circulation, with only an occasional pulsation, as shown in the kidney tracings. From all this it is clearly deducible that the local but extreme variations in the renal circulation were accompanied with but moderate and always transient effects upon the general blood-pressure.

EXPERIMENT 3. April 27th. Normal dog, weight 6.670 kilos, but of small size, and with a small kidney. The dog took both morphine and ether badly. After he had received 20 c.c. of antistreptococcus serum a trace of albumin appeared in the urine. The urine rapidly diminished in quantity, but no blood appeared in it, though some corpuscles were seen by microscope. The urine became highly albuminous after 50 c.c. of the serum were injected. The general renal tracings ran low, as in the other experiments, but varied more in irregularity of effects of morphine and of ether.

EXPERIMENT 4. April 29th. Normal dog, weighing 10 to 60 kilos, bore anæsthetics well. As time does not allow, I do not need to describe the tracings up to his receiving 35 c.c. serum injections, as they show a general correspondence with the others, especially of Experiment 1. He received in all 50 c.c. Urine became albuminous after 35 c.c., with suppression after 50 c.c., but at no time showed blood.

These experiments would seem to indicate plainly that large doses of antistreptococcus serum, administered hypodermatically and rapidly, do produce intense venous congestion of the kidneys, with albuminuria, and in some cases hæmaturia and hæmoglobinuria, with finally suppression. Pathologically the kidneys were found by Dr. Ewing so show: the arteries not enlarged, but the veins throughout dilated and full. It must be remembered, however, that the quantities administered in the above experiments were much in excess, in proportion to the weights of the animals, of anything which would be administered to human beings for remedial purposes.

The question, therefore, occurred to us whether the injection of any serum might not affect the renal circulation, and accordingly we have made experiments upon two dogs, one into which normal horse serum was injected twice a day for seven days, and another was first injected on the table, as with the experiments with antistreptococcus serum. These experiments we propose to supplement by others, as in both cases a generally similar effect to the antistreptococcus serum, but much less marked, was produced, including pathological appearances in the kidney.

One interesting observation was made on a dog infected for us by Dr. W. H. Park, at the laboratory of the New York Board of Health, with streptococci, on April 17th, 50 c.c. of a virulent culture having been injected into a vein. The next morning, the 18th, the dog presented serious symptoms of poisoning, and streptococci were found in the blood. Twenty-four hours after the dog had been infected, 20 c.c. of antistreptococcus serum were injected. The dog soon began to improve, and on April 20th the dog was apparently cured. Blood drawn from him, on his being sent to us that day, was examined, and no streptococci were found. His urine showed a faint trace of albumin. The tracings, both of the general circulation and of the oncometer, were those of a normal dog.

On the other hand, we tried the effects of gradual dosing with antistreptococcus serum, the results of which we propose to publish later. In one dog 50 c.c. in all of serum were injected: on April 20th 10 c.c., A.M., April 21st 10 c.c., A.M., and 20 c.c., P.M., and on April 22d 10 c.c., A.M. Both kymographic tracings in him were very nearly normal. His urine was diminished in quantity, and the urine showed very little albumin and no blood. In this case the whole dose was

large, but divided, with consequently much less effect upon the kidneys.

DISCUSSION.

DR. JAMES TYSON: A very remarkable case which was under my care for twelve months has been suggested by the report of these cases. A man living in a distinctly malarial district near Philadelphia was seized with chills and fever during the cold season, I think about Christmas time. The chills recurred on two or three successive nights, and the diagnosis of malaria was reasonably made by the physician in attendance. He failed, however, to improve upon the administration of large doses of quinine, and finally was taken to the University Hospital. The Widal test was made, but with negative results. He came under my care at the hospital, and the diagnosis was successively made as malarial fever, miliary tuberculosis, and ulcerative endocarditis.

The feature which has seemed to me to be the most constant, though still unsatisfactory in the pathology of endocarditis, the extreme irregularity of the chills and fever, was present in this case, by which I mean a chill at one time one day and at another the next. To be sure, in miliary tuberculosis we have this, but without such frequent recurrences of the chills. There were no physical signs of endocardial trouble, and no signs of lung trouble. The blood was frequently examined for malarial organisms, always with negative results, except in one instance, when a doubtful positive result was reported. For three months he was under my observation, and we were just about to institute the use of antistreptococcus serum when he began to improve. In a month or six weeks he was well, and, so far as I know, is well to-day. I was never more confident that I had a case going to fatal issue than in this instance, but he recovered, and not because of anything that was done for him. I presume the case was one of malarial fever.

DR. W. H. DRAPER: I would like to ask Dr. Thomson whether it is not possible that the hæmaturia observed during the last days of the patient's life was due, not to the injections of streptococcus serum, but rather to the occurrence of infarctions in the kidney resulting from embolic accidents. I have several times seen the complication of hæmaturia in cases of infective endocarditis where suspected embolic infarctions were verified post mortem.

DR. A. JACOBI: I arise to ask for information from those who are better informed. I have never seen cases of ulcerous endocarditis getting well. They all died; there are some in which diagnosis cannot be made, because the coccus deposits are near the insertion of the valves, but not at the margins. Cases of septic pyæmia, however, not complicated with endocarditis, are apt to get well. I have seen three such lately. In all of the three blood examinations were

made, and that is the point I want information about for diagnostic purposes. In all staphylococci were found, and in one only a few streptococci with the staphylococci. In my last case a well-informed friend told me that my diagnosis was not worth anything, and that the work I had done was useless, because there were always cocci to be found in the skin, and he had no doubt that I had removed them with the blood from the fingers in my careless way of sterilizing that finger. What I did in that case was to wash the finger with alcohol, sterilize the needle, and transfer the culture at once to the incubator. In order to find out whether I had made such a grave mistake, I have since made a number of blood cultures from healthy persons, using the same precautions that I did in that case of sickness; simply rubbing the fingers with alcohol for a few minutes, and then proceeding to draw the blood, and I have never found the cocci.

Now I want to know whether the plan I followed is sufficiently reliable for practical purposes. I know it is not such as would be followed in the laboratory, but in the interests of physicians in general practice I want to know whether this plan is sufficient for practical purposes.

DR. J. E. GRAHAM: I would like to mention two cases of septicæmia treated by antistreptococcus serum. One was a child who had had scarlet fever followed by suppuration of the ears, and who some weeks afterward developed symptoms consisting of a rigor followed by high fever, the temperature running as high as 105°. I called into consultation Dr. Cameron, and as quinine had been tried we agreed to try the serum. The temperature fell promptly, and the child recovered. About the time that injection was made, or a few hours before, a blood culture was made by Dr. Harris, now an assistant to Dr. Flexner, at the Hopkins University, and he found a pure culture of the staphylococcus pyogenes aureus. Cultures taken a week later showed no organism in the blood.

The second case was that of a young man who had been treated for malaria. He had been employed in a lumber camp in the northern part of Michigan, and had been taking large doses of quinine without any success. I was called to see the patient, and thought it necessary to have a blood culture made. This was done by Dr. Goldey, who has made a number, and does it very carefully, and he found the staphylococcus in large numbers. We gave the antistreptococcus serum in large doses, and repeated it on two or three occasions. In that case there was no rigor after the administration of the serum. He also recovered. In neither of these cases was there any heart lesion discovered, although carefully looked for. In the second case there was a little tenderness on the inner side of one thigh, that was the only point under suspicion.

DR. S. J. MELTZER: I wish to corroborate the statements of Dr. Thomson in regard to the effect of ether upon the kidneys. In the last two years I have had the opportunity to observe quite frequently the suppressing effect of ether upon the secretion of the kidney. I observed it in the experiments

I made to determine whether a certain substance appears first in the lymph or the urine; when using ether for anæsthesia I often could not obtain any urine at all. I have, therefore, frequently used for such experiments an anæsthetic quite commonly employed in the laboratories in England, which is a mixture of alcohol, ether, and chloroform. It does not have such a depressing effect upon the kidney. On the other hand, I may say that while ether has a depressing effect during the experiments, I have never seen any lasting effects upon the kidney from its use. This would lead me to think that even if it can be established, as Dr. Thomson has said, that by introducing serum into the animal a certain effect is produced upon the bloodvessels of the kidney, it is not thereby proved that it produces a permanent alteration in the kidney.

I did not hear exactly whether these injections were made hypodermatically or intravenously.

DR. THOMSON: Hypodermatically.

DR. MELTZER: I wish to mention some experiments of my own with regard to this question. In studying the erythrocidal effect of alien blood I have not only used serum, but the blood of other animals introduced intravenously in making the following experiment: I introduced the blood of an ox into the abdominal cavities of dogs and rabbits, left it there for three hours, then took it out, strained it and injected it into the jugular vein of another dog or rabbit. It was surprising to observe how little ill effect it produced upon this animal. The blood of the ox had, during the three hours while it remained in the peritoneal cavity of the dog, apparently acquired the qualities of the dog's blood. I state this to show what a distinct difference there is between introducing serum directly into the bloodstream or only into the subcutaneous tissue. In the latter place it remains there long enough to be effectively changed before being absorbed into the circulation.

In regard to the case reported by Dr. Thomson, it seems to me that there is no sure proof that it was exactly ulcerative endocarditis. The man, I understand, had a congenital cardiac malformation. No autopsy was made. The man may have had a cryptogenetic streptococcus infection. Somewnere in the body there may have been a focus that supplied the streptococcus, while the cardiac symptoms were produced by the congenital condition. This is merely a suggestion.

DR. THAYER: Dr. Thomson's statements with regard to the similarity of the temperature-curve in this case with that of quotidian malarial fever is very interesting. I have observed this remarkable similarity in a number of instances, and yet, if the patient be in such surroundings that the temperature can be frequently taken and accurately recorded, one may almost always note distinct differences between the fever in malarial infection and sepsis.

The paroxysms in sepsis are rarely absolutely regular in the hour of their onset, and are often very variable in their length.

In malaria, on the other hand, though it is quite possible for paroxysms due to one group of parasites to occur at different hours with succeeding periods of sporulation, anticipating or retarding considerably, it is, however, extremely unusual for such paroxysms to anticipate with one sporulation and retard with the next. If there be a tendency toward anticipation or retardation, it is usually more or less constant. If the chill occur say at 9 on Monday, at 7 on Wednesday, and at 10 on Friday, such irregularity is strong presumptive evidence against malarial fever. Slight irregularities of this sort are, I believe, almost always present in the septicæmia that simulates malaria.

There are also several other points which may tend to help us out in doubtful cases. In some grave septicæmias anæmia may be a prominent symptom, as it is in malaria. But in a good many instances, as in Dr. Thomson's case, this does not occur. I know of no variety of malarial infection which can exist with daily paroxysms for any considerable length of time without producing an anæmia graver than that occurring in this instance.

Again, most cases of septicæmia simulating malaria show well-marked leucocytosis, and even in cases where the increase in leucocytes is slight there is still, as a rule, a tendency toward an excess in the percentage of polymorphonuclear leucocytes. But in all varieties of uncomplicated malarial infection there is usually a subnormal number of leucocytes, while the diminution in the relative proportion of polymorphonuclear leucocytes is striking.

The therapeutic test is, I believe, positive. There is no form of malarial fever existing in our climate in which quinine fails to break the fever within four or five days, with the exception of occasional instances of rapidly fatal pernicious infections, in which death occurs before the drug has had time to act. Recovery invariably follows the use of the specific. One of the most important results of the discovery of the malarial parasite is, I believe, the proof which it has afforded us of the specificity of quinine.

Dr. F. C. Shattuck: I wish simply to say a few words with regard to the possibility of recovery from infective, ulcerative, or malignant endocarditis. It seems to me that it is rather venturesome to say that such cases cannot get well. Twenty years ago it was held that recovery from tubercular peritonitis was impossible, and we have seen other similar hasty generalizations overthrown. As in the case of every other infection, one must not have too much of it. Of course, if the patient recovers, post-mortem evidence falls out. I have seen a patient recover from what, with due skepticism, seemed to me to be malignant endocarditis. Having recovered, there is no proof that it was such. There are two other points to which I should like to allude: one is, that this process is more likely to attack an already damaged valve than one in perfect condition; and, in the second place, quite often the diagnosis of infective endocarditis must be made from symptoms entirely outside of the heart.

DR. THOMSON: With reference to the point made by Dr. Jacobi, that the blood might have been infected by cutaneous micrococci, that was the particular thing which we took pains to guard against by having the blood drawn from the median vein with very careful precautions.

As to the question of Dr. Meltzer, that the case may not have been one of infective endocarditis, but a septic one from some other focus, I can only say that the patient was examined constantly for signs of some other focus, and there seemed to be none present. I have had other cases of septic endocarditis that presented general symptoms similar to this, but none in which the focus was elsewhere than in the heart.

With reference to the remark of Dr. Draper, that the antistreptococcus serum may have had nothing to do with the final hæmaturia, I have no doubt that may be true. The reasons why we instituted these researches was rather to settle the point as to whether the antitoxins might have such an effect that their use would be contraindicated.

I was much interested in Dr. Thayer's remarks, but I would say that in this case it was remarkable how closely periodical the paroxysms were: I have seen many cases of periodicity in infective endocarditis, but I never saw a case that continued for such a length of time in which they were so markedly periodical as in this case. I agree with the statement that we need have no faith in a case being malaria, if it does not submit to quinine.

A COMPARATIVE STUDY OF BOVINE TUBERCLE BACILLI AND OF HUMAN BACILLI FROM SPUTUM.

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THE absolute identity of tubercle bacilli infecting mammalia has been so generally assumed and the assumption used as a basis for the enactment of sanitary measures having for their object the prevention of any transmission of tubercle bacilli from animals to man, that any one who would attempt to question this identity must be prepared to meet considerable seepticism. Taking a broad biological position, we have every reason to examine into the assumed identity of the bovine and the human bacillus, because both the human and the bovine species are victims of a tuberculosis, presumably transmitted in most cases from one individual to another of the same species, and because the adaptation of a highly parasitic organism to one of these species for centuries may possibly deprive it of much of its power to multiply in the other. Or the reverse may be true. The adaptation of the bovine bacillus to a larger, more vigorous organization may thereby render it more dangerous to man. Assumptions of this sort stimulate inquiry, but do not furnish us with positive information. This can be gained only by most tedious investigation.

In 1896 I presented to the Association of American Physicians[1] a comparative study of a bovine bacillus and a presumably human ba-

[1] TRANSACTIONS OF ASSOCIATION OF AMERICAN PHYSICIANS, 1896, xi. 75.

cillus which had passed from a tuberculous subject to an animal pet (*Nasua narica* "Coati"). The differences which appeared during this work were so clear, both as regards morphological and biological characters, that a further study was indicated. Imbued with the idea that in the minor, though constant, differences of closely related or apparently identical pathogenic bacteria many unexplained phenomena may have their source, and that a comparative study of tubercle bacilli under as nearly the same conditions as can be maintained may lead to results of value to human pathology, I took up the subject anew. A consultation of the literature treating of the character of tubercle bacilli had impressed me with the carelessness shown by most writers subsequent to Koch, concerning the source of the cultures used by them. Papers written on methods of cultivating the presumably human bacillus were really devoted to the avian bacillus. Fischel,[1] though drawing far-reaching conclusions on the relation of human to avian bacilli, makes no statement concerning his cultures save that they were "mammalian."

There being, therefore, no information to be gathered from former publications, the task that presented itself was to study a number of human and bovine bacilli, and if possible tubercle bacilli from other mammalia, side by side, in order to determine whether constant differences of whatever nature could be demonstrated. Such differential characters might then be applied in studying different forms of human tuberculosis, especially those cases which are supposed to have been derived from animals, more particularly from cow's milk.

The delay inseparable from the study of this disease has not permitted me to examine more than a limited number of cultures. Including the two described in 1896, seven sputum and six bovine cultures have been isolated and studied; also one animal culture presumably derived from sputum, one culture each from the horse, the cat, and the pig.

In Table I. are given brief accounts of the subjects from which they were obtained. For the notes on the cases of phthisis I am indebted to a number of physicians who have very generously given their time in tracing the subsequent history.

[1] Fortschr. d. Med., 1892, x. 908. See also my former article for further references.

TABLE I.

Designation of culture.	Beginning of artificial cultivation.	Source of culture.	History of case.
Sputum I.	July 20, 1896	Peabody, Mass.	Sputum discharged June 24, 1896, by a young Irish woman. Apex and upper lobe of left lung involved. Slight fever. Sputum contains a considerable number of bacilli. Recovered and worked during summer. Good health in the fall of 1896, with gain in weight. February, 1898, in good health; works daily. No cough, expectoration, or other symptoms of illness. Over the formerly involved region "the respiratory murmur much diminished down to third rib. Increased vocal resonance, increased fremitus and dulness on percussion." Patient has moved from place to place.
Sputum II.	Nov. 21, 1896	New Bedford, Mass.	Sputum containing many tubercle bacilli discharged October, 1896, by a young man confined in prison about one year. Earliest appearance of symptoms not accurately known. Slight cough noticed in August, 1896, but no definite physical signs at that time. Grew steadily worse, so that in November he was in bed, weak and emaciated, and also suffering with diarrhœa. He died in March, 1897.
Sputum III.	Feb. 15, 1897	Norwood, Mass.	Sputum discharged January 12, 1897, by a man aged forty-five years. Duration of disease about six months. Laryngeal tuberculosis chiefly. Difficulty in swallowing, and huskiness of voice, which has been gradually increasing. Died February, 1897. The physician in charge had drawn about a litre of serum from the thorax four or more years ago; well thereafter until fall of 1896. Apex of lungs slightly involved toward end of disease. Patient has travelled much in this country.
Sputum IV.	Feb. 16, 1897	Melrose, Mass.	Sputum containing but relatively few bacilli discharged January 7, 1897, by a female servant, twenty-two years old. Physician in charge saw her first December, 1896. She complained of hoarseness and cough which began about six months ago. Signs of anæmia and cessation of menstrual flow. Placed in hospital, where she remained eight weeks. At end of April health quite re-established. A subsequent report mentions her visit to Canada after her recovery, and her return to Massachusetts. She is now (January, 1898) at service in another town. She has a troublesome cough and is under the care of a physician.
Sputum V.	July 7, 1897	New Hampshire	Sputum discharged June, 1897, by a man twenty-five years old. Had been troubled with a cough for about two years, and apices reported involved. Patient feels well in the country, but cannot carry on his trade (printer) in the city. In January, 1898, he was reported to be much improved in every way.
Sputum VI.	July 14, 1897	Winthrop, Mass.	Sputum discharged June 16, 1897, by a woman twenty years old. Tubercle bacilli numerous. History not obtainable. Patient died about six months later.
Sputum VII.	Jan. 18, 1898	Haverhill, Mass.	Sputum containing many bacilli discharged by an Italian laborer December 15, 1897. Age of patient twenty-seven years. Returned to Italy in January, 1898.
Nasua narica (Coati), human sputum(?)	July 26, 1894	Washington, D.C.	Autopsy, May 12, 1894, revealed primary intestinal infection, as mesenteric glands were furthest advanced in the disease. Omentum studded with tubercles. Extensive embolic tuberculosis of lungs. Household pet of tuberculous man. At Washington Zoological Park, where animal was kept after death of owner, other animals of same species remained well.

Designation of culture.	Beginning of artificial cultivation.	Source of culture.	History of case.
Bovine I.	Dec. 1, 1894	Virginia.	Bull with advanced generalized disease. Great enlargement of lymph glands of head and thorax. Tuberculosis of the bones. Periodic tympanites due to enlarged mediastinal glands. Killed.
Bovine II.	Nov. 28, 1896	Lawrence, Mass.	Cow having multiple necrotic foci in large caudal mediastinal gland. Foci dry, cheesy; process evidently old In one lobe of lung a focus 1½ inches in diameter with centre softened. In udder small nodules containing actinomyces. Killed.
Bovine III.	Apr. 19, 1897	Carlisle, (?) Mass.	Cow killed March 19, 1897, at Brighton (Boston) abattoir. Quite extensive disease of lungs and liver.
Bovine IV.	Apr. 23, 1897	Billerica, Mass.	Cow killed March 19, 1897, at Brighton abattoir. Disease restricted to one of dorsal mediastinal glands. The gland is moderately enlarged and contains a number of well-defined tubercles, 3 to 4 mm. in diameter, dry, cheesy throughout, and easily peeled out of gland tissue. No surrounding infiltration. Evidently a mild stationary case.
Bovine V.	Apr. 23, 1897	Carlisle, Mass.	Cow killed March 19, 1897, at Brighton abattoir. Disease has produced a focus in the lungs, and involves all dorsal mediastinal glands, which are considerably enlarged. One of the portal glands is enlarged and permeated with a network of necrotic lines.
Bovine VI.	Dec. 24, 1897	Newton, Mass.	Caseous matter from a focus in the lungs of a cow two to three years old. The focus several inches in diameter, probably not more than three to three and a half months old, since the cow gave no tuberculin reaction four months ago. Dorsal mediastinal gland involved.
Swine I.	May 8, 1896	Southboro, Mass.	Lungs and one gland (presumably from mesentery) received at laboratory March 18, 1896. The herd lived under a cow stable, and the infection was probably bovine in origin. Lungs studded with firm, centrally cheesy or calcified nodules from 1 to 4 mm. in diameter. The lymph gland contained many foci with cheesy centres.
Cat I.	Mar. 9, 1897	.....	Case reported by L. Frothingham, V.M.D., in the Journal of the Boston Society of Medical Sciences, March, 1897. Tuberculosis of a mesenteric gland with miliary tuberculosis of lungs, liver, and spleen. Tubercle bacilli in capillaries of lungs and liver. Guinea-pig inoculated by Dr. Frothingham, and kindly transferred to me.
Horse I.	Feb. 20, 1897	.....	Lungs of a horse from Brighton rendering establishment. Guinea-pig inoculated from tubercles by Dr. L. Frothingham. History of animal not known.

It will be noticed that these cultures come from a variety of cases, both mild and severe. Of the patients yielding the sputum bacilli, three are dead, two still sick, one has apparently recovered, and one, a recent case, is now not accessible. Of the bovine cases, two were slight, two advanced, and two of moderate intensity. Of the other mammals nothing very definite is known.

The bacilli were isolated in all cases by inoculating guinea-pigs

with tuberculous tissue or sputum containing bacilli. With sputum the injection of a suspension in bouillon into the abdominal cavity is the most satisfactory. Subcutaneous inoculation may induce a very chronic disease with older (500-gramme) guinea-pigs, which is not so likely to lead to successful cultures because of the scarcity of bacilli in the tuberculous foci. In nearly all cases the guinea-pigs were chloroformed after three or four weeks to prevent secondary infections occurring in the final stages of the disease.

Inasmuch as a more general study of tubercle bacilli is desirable, I shall go somewhat into detail concerning the methods I have employed in making cultures. Having had practically nothing but failures until I adopted the procedure to be described, I can recommend it without reserve. There is nothing new about it, excepting in the combination of details. Of eighteen attempts to isolate the bacillus seventeen were successful. The one failure was probably due to the slow process of the inoculation disease in the guinea-pig.

Throughout the work dog's serum was used. The dog was bled under chloroform and the blood drawn from a femoral artery under aseptic conditions, through sterile tubes directly into sterile flasks. The serum was drawn from the clot with sterile pipettes, and either distributed at once into tubes or else stored with 0.25 to 0.3 per cent. chloroform added. Discontinuous sterilization was rendered unnecessary. The temperature required to produce a sufficiently firm and yet not too hard and dry serum is for the dog 75° to 76° C. For horse serum it is from 4° to 5° lower. The serum was set in a thermostat, into which a large dish of water was always placed to forestall any abstraction of moisture from the serum. About three hours suffice for the coagulation. When serum containing chloroform is to be coagulated I am in the habit of placing the tubes for an hour or longer into a water-bath of 55° to 60° C., or under the receiver of an air-pump to drive off the antiseptic. This procedure dispenses with all sterilization excepting that going on during the coagulation of the serum. It prevents the gradual formation of membranes of salts, which, remaining on the surface during coagulation, form a film unsuited for bacteria. Tubes of coagulated serum should be kept in a cold closed space, where the opportunities for evaporation are slight. They should always be kept inclined.

The ordinary cotton-plugged test-tubes I do not use, because of the rapid drying out permitted by them, as well as the opportunities for infection with fungi. Instead a tube is used which has a ground-glass cap fitted over it. This cap contracts into a narrow tube plugged with glass wool. This plug is not disturbed. The tube is cleaned, filled, and inoculated by removing the cap. With sufficient opportunity for the interchange of air very little evaporation takes place, and contamination of the culture is a very rare

occurrence. In inoculating these tubes bits of tissue, which include tuberculous foci, especially the most recent, are torn from the organs and transferred to the serum. Very little crushing, if any, is desirable or necessary. I think many failures are due to the often futile attempts to break up firm tubercles. Nor should the bits of tissue be rubbed into the surface, as is sometimes recommended. After a stay of several weeks in the thermostat I usually remove the tubes and stir about the bits of tissue. This frequently is the occasion for a prompt appearance of growth within a week, as it seems to put certain still microscopic colonies in or around the tissue into better condition for further development. The thermostat should be fairly constant, as urged by Koch in his classic monograph; but I look upon moisture as of more importance. If possible, a thermostat should be used which is opened only occasionally. Into this a large dish of water is placed, which keeps the space saturated. Ventilation should be restricted to a minimum. As a consequence moulds grow luxuriantly, and even the gummed labels must be replaced by pieces of stiff manila paper fastened to the tube with a rubber band. By keeping the tubes inclined no undue amount of condensation water can collect in the bottom and the upper portion of the serum remains moist. The only precaution to be applied to prevent infection with moulds is to thoroughly flame the joint between tube and cap as well as the plugged end, before opening the tube. When test-tubes are employed it is well to dip the lower end of the plug into sterile molten paraffin and to cover the tube with a sterilized paper cap. The white bottle-caps of the druggist are very serviceable.

In pursuing this method of obtaining cultures the question arises: May not attenuated or more saprophytic forms exist in the sputum besides those more pathogenic, and may not the former get into our cultures rather than the latter? This question cannot be answered with entire satisfaction. If we assume for the sake of illustration that the original disease was due to perhaps one inhaled bacillus, the progeny of this bacillus may be reinforced by others inhaled which have more saprophytic and less pathogenic tendencies, and which multiply in the cavities and in the sputum to the partial suppression of the original form. If we make cultures directly from sputum this hypothetical danger could not be evaded. The inoculation of the guinea-pig and the three or more weeks elapsing before cultures are made is to a certain degree a safeguard, as it gives the more pathogenic form an opportunity to assert itself by prompt multiplication. I am not inclined to look upon this danger of substitution as a real one. At the same time it may be best always to choose those successful cultures from the guinea-pig which have come from metastatic rather than local (peritoneal) tubercles. In my work I obtained in most cases cultures simultaneously from three or four organs, and any difference in these original cultures was not manifest. Only one was used in the comparative studies. Of seven sputum cultures two were derived from the omentum and four from the spleen. Of one the source is not noted. For the bovine cultures no such doubts can be raised, because the foci are closed and not accessible to more saprophytic types.

In the study of the various cultures the conditions were maintained as nearly uniform as possible by using tubes of serum prepared at the same time and keeping the inoculated cultures in the thermostat in the same trays. For the microscopical examination a little of the surface growth was rubbed between two cover-glasses, these allowed to dry in the air, and then the whole series to be compared were fixed all together in the hot-air sterilizer at 120° C. for twenty to thirty minutes. For staining, carbol-fuchsin was used cold, and the decolorization effected with a 10 per cent. aqueous solution of sulphuric acid acting for from fifteen to thirty seconds. Cover-slips were also decolorized with ½ per cent. acetic acid—some simply washed in water; others were stained according to Gram-Weigert. In all cases the members of the series studied were treated alike and at the same time, thus eliminating minor, often unavoidable, variations. In all cases the characters to be described refer to dog-serum cultures. These were renewed every three to six weeks, as many at a time as was possible. The regularity of reinoculations was now and then interrupted by a beginning infection of the tube with moulds or a too feeble growth, necessitating earlier transfer to fresh tubes. As a rule, the cultures were kept continuously in the thermostat until the next transfer was made.[1]

The tendency of most species of bacteria to vary slightly from tube to tube, either in size, form, or staining capacity, is also characteristic of tubercle bacilli, so that repeated examination of series of cultures is necessary to obtain what might be called a composite photograph of their most permanent characters or peculiarities. The statements made below as to the morphology of the bacilli under observation are based on the repeated examination of hundreds of slides, of which the conditions of growth of the bacilli, the coagulating point of the serum, and the staining manipulations had been carefully noted. The cultivation of tubercle bacilli requires, even under the best circumstances, constant personal attention, and those not prepared to give it had better not attempt it seriously. Success is obtainable along lines other than those suggested by me. Koch succeeded by using beef's serum in ordinary plugged test-tubes. He is, however, the only investigator, I believe, who has studied series of cultures of tubercle bacilli.

Morphological and Biological Characters.

With one exception, to be noted below (Sputum I.), the human bacilli grew from the start much more vigorously than the bovine bacilli. With several the rapidity of growth was surprising. After two weeks these cultures appear as a whitish surface layer of a pearly lustre, of varying thick-

[1] It is always desirable as a precautionary measure to retain three or four older transfers of any culture in a cool, dark place, so that it may not be lost through some accident or contamination. Now and then culture-media will prove unsatisfactory. In such cases the earlier tubes must again be resorted to. I have noticed that upon all the serum-tubes from one dog growth was feeble. The liver and the kidney of this animal showed considerable fatty changes, although the animal had not been ill. Possibly over-feeding may be the cause of the difficulty.

ness. The bovine cultures show merely discrete colonies, or a thin, uniform layer having the appearance of ground-glass.[1] This difference in the vigor of growth has, in general, maintained itself, with the slowly increasing tendency of all cultures to multiply more rapidly.

The size of bovine bacilli in the various cvltures was quite constant. They were all quite short, usually about 1 to 1.5 μ long, more rarely 1 to 2 μ. These measurements do not tend to change appreciably with prolonged cultivation. The bacilli are straight; not very regular in outline. Some are broader at one end than at the other, some broader in the middle than at either end—*i. e.*, spindle-shaped. Some may be so short as to resemble oval cocci. With the human bacilli the form was not so constant. The earliest cultures of Sputums II., IV., V., and VI. contained forms from 1 to 2 μ long, hence closely approximating the bovine forms. Others (Sputum III.) may be longer from the start. In all, however, there is a tendency, not noticed among bovine cultures, to grow longer under artificial cultivation. Perhaps the greatest contrast in form, which has remained so for three years, is illustrated by the bovine and the Nasua (human) culture described in 1896. In the latter the bacilli are from two to three times the length of the former.

In the earliest cultures, therefore, morphological differences are not necessarily characteristic, and cannot aid us in attempts at determining the origin of cultures. Cultures containing only small forms have been noted by Metchnikoff and Straus. The latter states that even the avian variety may assume very small dimensions under certain circumstances.

When the serum to be used for cultures is coagulated at a temperature of 71° to 72° C., instead of 75° to 76° C., certain modifications are manifest. All bacilli which have developed on a serum having a firm surface, and which is obtained at the higher temperature, absorb the dye promptly and become brilliantly stained. When a softer (71° C.) serum is employed, whose surface is easily depressed, torn and broken by the platinum needle, the culture, which may have become either more or less vigorous than before, now contains a large number (from 50 to 90 per cent.) of bacilli which stain quite feebly. Uniformly dispersed among them are deeply stained forms. This feeble stain is noticed when bacilli are not treated with decolorizing agents at all, and the appearance of the cover-slip preparation is not materially altered by the acid.[2]

While both human and bovine bacilli are affected by the softer serum, the former show a much greater degree of change. The bacilli are very feebly

[1] In some tubes a peculiar coppery discoloration may extend over the entire surface-growth. Cultures from these are fertile, however. There is nothing in the microscopical appearance of the bacilli to explain this change. It is not an uncommon feature of cultures of feeble vitality or of unsatisfactory culture-media.

[2] Since the completion of this manuscript further studies of this phenomenon have convinced me that at least some of the feeble staining is due to the formation of a capsular substance which interferes with the penetration of the dye. This substance, which is produced in greatest abundance by the human cultures, is not infrequently detected as a regular or an irregular unstained envelope around a single bacillus or a group. It is not stained by the procedure recommended by Prof. Welch for staining capsules.

stained and show outlines often very indistinct. Further than this, the human bacilli, on the softer serum, tend to become longer and slightly curved. In some cultures this change is very pronounced, in others less so. With the bovine forms there is no elongation, although the bacilli may be less brilliantly stained than on firm serum. Of seven human cultures studied, all have exhibited this tendency to become slender, while none of the bovine bacilli have been seen to change their size to any appreciable degree. Some of the bovine cultures from softer serum did not even show any feebly stained bacilli.

Another modification in form which manifests itself upon the firmer serum is the appearance of round, deeply stained bodies at or near the end of the usually slender bacilli, very rarely in the middle. These bodies, from 1.5 to 2 times the diameter of the rod, take a brilliant stain in carbol-fuchsin, contrasting with the more feebly stained, less compact rod in which they are embedded. These bodies, which have a striking resemblance to spores, may be present in all the rods of any one preparation, or in a certain proportion only. They have been seen in Nasua, Sputum III., IV., and VI. In the bovine cultures bodies of this nature are occasionally recognizable; but owing to the shortness of the bacilli, they do not stand out distinctly. Of much more frequent occurrence in these cultures, often the only forms present, are short fusiform or spindle-shaped rods, the central swelling being also deeply stained, and perhaps corresponding to the terminal body of the human forms. These bodies have been seen by Ehrlich, Nocard and Roux, Metchnikoff, Cornil and Babes, Czaplewski and Straus. They have been variously interpreted as spores, and bacilli containing them have been successfully double-stained. Their significance remains unsolved. The most probable explanation is a degeneration or involution form. They may, however, represent some resting stage, and correspond to the short brilliantly stained bodies frequently seen in giant cells, and not recognizable as bacilli. In unstained films, mounted in water, they cannot be distinguished even with a very narrow pencil of light. An increased refrangibility cannot be made out.

Experiments to determine the length of time required at 60° C. to destroy both human and bovine forms have thus far not revealed any differences. The tests are reserved for a special publication.

A study of the relative resistance of the bacilli to drying has not yet been attempted.

Among the sputum cultures is one (No. 1) which grew so feebly on dog's serum that its cultivation was finally given up. The history of the case is briefly given in Table I. Since the comparative tests of the pathogenesis of this culture are very incomplete, I shall give briefly the results of the inoculation of the sputum as evidence that the organism was in reality a tubercle bacillus.

June 27, 1896. Guinea-pig, weight 640 grammes, receives into abdomen 0.5 c.c. of bouillon in which some sputum is suspended.

July 20th. Weight 457 grammes. Animal rather dull, with coat slightly staring. Very little resistance to handling. Chloroformed.

A few subserous tubercles around point of injection. Omentum represented by a cylindrical mass of neoplastic tissue, about 1 to 2 cm. in diameter, firm, speckled with whitish dots, indicative of necrosis. Tubercles on diaphragm and testicles. Liver spotted with small, irregular, not well-defined yellowish necroses. Spleen slightly enlarged, with Malpighian bodies prominent. Bronchial and sternal glands enlarged, with central necrosis. Lungs free from visible tubercles.

The pathogenic power of this sputum seems to have been equal to that of most sputa examined. One guinea-pig of 672 grammes, inoculated precisely like the preceding, died in forty-six days after inoculation, with more pronounced lesions of the liver and spleen. A third guinea-pig of 370 grammes, which had received the same quantity subcutaneously, weighed a trifle more on the forty-ninth day (390 grammes) than at the beginning. On this day it was chloroformed and examined. There was the typical ulcer with surrounding tubercles in the subcutis and few tubercles in the omentum. The liver was pale and fatty; the spleen enlarged to several times the normal size and uniformly permeated with grayish (1 mm.) foci, but without necroses. The lungs were studded with small, partly necrotic tubercles. The bronchial and sternal glands were large, with necrotic centres.

The first culture showed somewhat slender, but well-stained bacilli. In tubes subsequently inoculated the bacilli multiplied almost exclusively in the condensation water, which became milky in appearance. In this the bacilli appeared in roundish clumps among cholesterin crystals. The bacilli were embedded in a colorless material which formed the cohesive clump. The stained bacilli presented no unusual characters save in one culture (after about six months of total cultivation) in which fully one-half of all the quite slender bacilli appeared as series of transverse apparently unconnected stained blocks, simulating streptococci. It is unfortunate that more animal tests were not made with this stock. As I was expecting a more vigorous culture from month to month, tests were postponed until conditions should approximate those of the other cultures. These were, however, not realized. The only test upon a rabbit is given in Table III. The cultivation was finally abandoned.

Of the other animal bacilli the cultures from swine were identical with the bovine cultures in morphological and other characters. Those of the horse and the cat were also either identical with the bovine bacilli or they very closely resembled them.

If we undertake to summarize the observations made with microscope and culture tubes upon these bacilli we somewhat hesitatingly formulate the following general statements:

1. Bovine and other animal bacilli (except *Nasua*, which is regarded as coming from man) grew less vigorously for a number of generations

than the sputum bacilli. Sputum I. is an exception, and is probably an atypical form.

2. Bovine bacilli are much less influenced by certain modifications of the culture medium.

3. Bovine bacilli tend to remain short; human bacilli are either more slender from the start or become so during cultivation.

PATHOGENESIS.

The most important means of demonstrating identity or divergence of characters of pathogenic bacteria is the test upon animals. This test is a purely physiological one, but in the application of experimental results from the domain of bacteriology to medicine, morphological characters must give way to physiological.

That there might be differences among tubercle bacilli from different species of mammals presented itself as a possibility to Koch, and is referred to in his monograph. He, however, failed to recognize any differences worth mentioning. There are several reasons for this. In the first place, Koch was at that time endeavoring to prove to the world that the tubercle bacillus is the cause of tuberculosis. Minor details received no attention because of the great and difficult task immediately before him. In the second place, the course of tuberculosis is essentially a function of the number of bacilli introduced. Variations in the dose result in corresponding variations in the length of the disease, in its final termination, and in the extent and distribution of the lesions. This fact Koch himself recognized in discussing the results following the intraocular inoculation of varying quantities of culture material in rabbits. He did not, however, attempt to adjust carefully the quantity to be injected or to determine the effect of varying quantities of bacilli upon any of the species used by him. Curiously enough, no one following him seems to have considered it worth while to extend his work by more accurate comparative tests. That such work is likely to be fruitful the following experiments amply demonstrate.

Guinea-pigs. The inoculation of this species with tubercle bacilli from the various cultures brought out few well-defined differences. The great susceptibility of guinea-pigs to tubercle bacilli is responsible for the general acceptance of a common level of pathogenic power for all mammalian tubercle bacilli. This tendency to unify physio-

logical characters because of a more or less uniform action upon very susceptible species has led to frequent failure on the part of experimenters to recognize important variations among species of bacteria, variations probably having much influence upon the course of the disease contracted in the natural way. There are, however, certain differences in the action of bovine and sputum bacilli upon guinea-pigs which enable us to recognize even in these very susceptible animals the much greater virulence of bovine bacilli. It is probable that by a graded dosage of tubercle bacilli more marked differences might be brought out than I am in position to present.

It has already been stated that all the cultures in hand had been obtained by inoculating the tuberculous tissue or the sputum into guinea-pigs and isolating the bacilli from them. To obtain the bovine cultures, a small bit of tissue was placed in a subcutaneous pocket in the flank. For sputum bacilli, the sputum was shaken up in sterile bouillon and the dilution injected into the abdominal cavity. In these preliminary experiments, differences presented themselves between the two kinds of material. Although the sputum, as a rule, contained very many tubercle bacilli and the bovine tissue very few, yet the subcutaneous injection of sputum led to such a chronic disease with comparatively slight lesions and a tendency to reparative changes in liver that the animals were very unpromising subjects for culture when chloroformed.[1] Hence the intra-abdominal inoculation in most cases. On the other hand, the disease due to bovine tissue placed in the subcutis never failed to produce extensive lesions with indications of certain death in four to six weeks, which was anticipated by chloroform when cultures were to be made. Leaving this preliminary series of inoculations we will pass to those made with definite doses of tubercle bacilli in suspension.

The suspension was made by thoroughly rubbing the growth from blood serum upon the inside of dry sterile test tubes with a heavy spatula-like platinum wire. This procedure results in the breaking up of clumps and the coating of the tube with masses of bacilli. Bouillon was then poured in, and the thoroughly stirred suspension allowed to stand for several hours until all coarser particles had subsided. The resulting suspension was diluted if necessary until its density was nearly equivalent to that of a bouillon culture of typhoid bacilli twenty to twenty-four hours old, and nearly as homogeneous. More accurate dosage might be obtainable by weighing the moist growth before suspending it in bouillon. But inasmuch as the weighed quantity may not all be brought into a finely divided state—a matter of importance in the intravenous injection of rabbits—the method adopted is probably less troublesome and equally accurate.

Of this suspension the usual dose, both for subcutaneous and intra-abdom-

[1] These statements apply only to guinea-pigs weighing 400 grammes and above.

inal inoculation, was 0.5 c.c. An examination of the dates in the various tables will show that many of the inoculations upon rabbits, guinea-pigs, and cattle were made with the same suspension on the same day.

The guinea-pigs employed were all rather large, weighing, with few exceptions, from 400 to 700 grammes. They had all been used in diphtheria antitoxin tests one to three months before. The rapid increase in weight was evidence of no disturbance of health at the time of inoculation. It is of importance to bear in mind that the animals were large, because the progress of tuberculosis differs essentially in growing and adult guinea-pigs, the latter manifesting a far greater resistance than the former, a resistance expressed by well-marked reparative or cirrhotic changes in the liver. The differences to be pointed out in the bovine and sputum series may possibly be nearly wiped out by the use of guinea-pigs weighing only 250 to 300 grammes.

The disease induced by the intra-abdominal injection was so rapid in its progress for both bovine and sputum cultures that the virulence of both races appears nearly the same.

The shortest period between inoculation and death when 0.5 c.c. of the suspension was injected, is seven days, the longest twenty-one days, with one exception, that of Sputum VI., which was thirty-eight days. In other cases the period was prolonged because of smaller doses. For Bovine I. (0.2 c.c.) it was thirty-three days; for Nasua (0.3 c.c.) forty-one days. If we take the largest series in which the injections were made at the same time and in which the conditions were identical—the series comprising cultures of Sputum IV., V., VI., and of Bovine III., IV., V.—we find the periods elapsing between inoculation and death to be respectively twenty-one, eleven, and thirty-eight days for the sputum, and seven, nine, and ten days for the bovine cultures.

The disease due to the intra-abdominal injection of tubercle bacilli in the quantity used is peculiar in this: that there is always found after death a large quantity of an opalescent fluid in both pleural sacs. This fluid greatly compresses the lungs, and is probably the immediate cause of death. When the disease is prolonged beyond three weeks the pleural effusion is absent. A careful histological study of the various organs in this most acute form of the inoculation disease, which will probably furnish the explanation of the effusion, is still to be made. In the abdominal cavity there is, as might be expected, a general inflammation of the peritoneum, associated with some fibrinous exudation and usually a little viscid fluid when the disease does not last quite ten days. Any prolongation beyond this brings a dense eruption of tubercles into view. The omentum is in all cases represented by a cylindrical mass of fused tubercles.

If we turn to the subcutaneous inoculations, the difference in pathogenic power is more clearly brought out.

In the same series just quoted, of the three sputum guinea-pigs, one died forty-four days after inoculation; the others were chloroformed respectively seventy-seven and one hundred days after inoculation, the first having lost but little in weight, the second being a trifle heavier but having extensive pulmonary disease. The bovine guinea-pigs died in fifty-one, forty-one, and forty days respectively. The sputum guinea-pig which succumbed in forty-four days weighed at the start 130 grammes less than the lightest bovine guinea-pig. The lesions were slight, the lymph glands only moderately enlarged, the foci in the lungs not visible to the naked eye. The spleen was not enlarged. The liver was mottled with very many grayish specks. The microscopic examination showed lesions but slightly advanced and reparative changes with proliferation of bile ducts in progress. In general, the tuberculous lesions in this animal did not warrant so early a death.

The histological examination of the tissues of the infected guinea-pigs was restricted to the lungs and the liver of those inoculated simultaneously under the skin with cultures of Sputum IV., V., and VI.,[1] and of Bovine III. and V. These organs were chosen because of their peculiar behavior toward the infection. The liver is invaded first, and under favorable conditions cirrhotic changes may begin, which in some cases apparently lead to an elimination of the disease, with considerable shrinking of the organ and furrowing of the surface. In the lungs the disease begins later, and if the animal survives the first six weeks, may grow steadily until most of the organ is involved.

Pieces of tissue hardened in Zenker's fluid or alcohol were cut, embedded in paraffin. The sections, fastened to the slide with Mayer's albumen and water combined, were stained with hæmalum and eosin or picro-acid fuchsin, or with eosin and methylene-blue. In some cases Weigert's fibrin stain was resorted to. All were stained for tubercle bacilli in carbol-fuchsin, differentiated in 1 per cent. acetic or decolorized in 4 per cent. sulphuric acid, and stained subsequently in Loeffler's methylene-blue. The stain for tubercle bacilli was successful in the tissues hardened in Zenker's fluid. Even in the sections stained according to Gram-Weigert the bacilli appeared distinctly, but in a peculiar form, often simulating short streptococci with the individual cells rather well separated, or series of short blocks with spaces between them. Here the stain fastens itself only upon certain segments of the bacillus, leaving the connecting elements entirely unstained. The part selected evidently stands in no relation to the bulging, deeply-stained, spore-like bodies referred to above as occurring in cultures.

In discussing the histological changes induced by tubercle bacilli in the various animals inoculated, it has been my determination to steer clear of all controversial questions relating to the histogenesis of the tubercle, or of the elements composing it, as being foreign to the scope of this etiological study. Only those features will be very briefly referred to which show pro-

[1] Spleen in place of liver in this case, the latter having been rejected by mistake.

nounced variations and which serve to point out differences in the action of the bacilli.

In the liver of the inoculated guinea-pig the proliferative lesions present in all cases examined consist of aggregations of the characteristic epithelioid cells, among which, here and there, scattering nuclei appear richer in chromatin, and which for convenience are designated lymphoid elements. The lesions, situated chiefly in the interlobular tissue, are surrounded with a wide or narrow zone of proliferating bile-ducts, which appear as single or forked lines or in the form of meshes. There is nothing in the microscopic appearance of the liver tubercles to serve as distinguishing marks excepting the much more extensive involvement of the liver-tissue and the much greater abundance of tubercle bacilli in bovine cases. In the latter there are added to these lesions those of another character, the simple necrosis of cell territories ushered in by the fading out of the nuclei and a deep stain with eosin. These areas probably represent the yellow cheesy areas so common, and often very large, in young tuberculous guinea-pigs. They are readily distinguishable with the naked eye from the grayish proliferative changes going on in the interlobular tissue. In the sputum cases the very rare areas of this character seen were very small.

In the lungs the lesions are, as a rule, perivascular and peribronchial. There are no essentially distinctive features here excepting the very great abundance of tubercle bacilli in the bovine cases. In Bovine III. the bacilli are also found in large numbers in cell detritus occupying alveoli and small bronchi. In Sputum VI. many alveoli in the periphery of the foci are nearly filled out with multinucleated cells, resembling giant cells closely, but their contents are only pigmented particles. In Bovine V. similar cells are present, though in small numbers. These as well as other cells in the alveoli each contain several bacilli.

The action of tubercle bacilli from the pig, the horse, and the cat upon guinea-pigs was nearly the same as that of the bovine cultures, and needs no special discussion here.

With this hasty, imperfect sketch we may conclude the notes on the tuberculosis of guinea-pigs induced with cultures by simply adding that the bovine bacilli studied are more virulent than human bacilli, although, owing to the great susceptibility of this species, the differences are not likely to impress us unless we give much attention to experimental details. These differences may be summed up as consisting in the more rapid death of all guinea-pigs inoculated with bovine bacilli, the greater extent of the lesions and the far greater abundance of tubercle bacilli in them.

In Table II. will be found in part the basis for these conclusions.

TABLE II.—GUINEA-PIGS.

Culture.	Total age of artificial culture.	No. of transfer.	Date of inoculation.	Age of culture in days.	Dose in c.c.	Mode of inoculation.	Initial weight in grammes.	Final weight.	Result.
Sputum I.	No inoculation of cultures.	.....	(Of sputum suspension) June 27, 1896	.....	0.5	Intra-abd.	672	430	Dies August 11th–12th.
					0.5	Subcut.	370	390	Chloroformed August 15th (active).
					0.5	Intra-abd.	640	457	" July 20th (sick).
" II.	3 months, 3 days.	5th	Feb. 24, 1897	24	0.5	Subcut.	570	520	" April 19th.
					0.5	Intra-abd.	600	...	Dies March 6th–7th (ten to eleven days).
" III.	5 " 10 "	8th	May 1, 1897	9	0.5	" "	440	312	" May 13th (thirteen days).
	1 " 19 "	2d	April 3, 1897	18	0.5	" "	525	...	" April 12th–13th (nine days).
	2 " 17 "	4th	May 1, 1897	9	0.5	" "	435	245	" May 17th (seventeen days).
	2 " 17 "	2d	May 1, 1897	18	0.5	" "	705	...	" May 15th–16th (fifteen days).
" IV.	6 " 10 "	7th	Aug. 26, 1897	9	0.5	Subcut.	372	275	" October 9th.
	6 " 10 "	7th	Aug. 26, 1897	9	0.5	Intra-abd.	507	...	" September 16th–17th (twenty-one days).
" V.	1 " 19 "	3d	Aug. 26, 1897	9	0.5	Subcut.	458	402	Chloroformed December 3d.
					0.5	Intra-abd.	517	...	Dies September 5th–6th (eleven days).
" VI.	1 " 12 "	3d	Aug. 26, 1897	9	0.5	Subcut.	420	431	Chloroformed Nov. 11th; extensive lung
					0.5	Intra-abd.	478	338	Dies Oct. 3d (thirty eight days). [disease.
" VII.	1 " 10 "	2d	March 1, 1898	16	0.5[1]	Subcut.	323	360	" May 14th–15th.
					0.5[1]	Intra-abd.	332	222	" March 18th–19th (eighteen days).
Bovine I.	15 " 19 "	14th	Mar. 20, 1896	16	0.5	Subcut.	405	?	Chloroformed May 14th (failing).
					0.2	Intra-abd.	478	...	Dies April 22d (thirty-three days).
" II.	2 " 27 "	3d	Feb. 24, 1897	24	0.5	Subcut.	580	?	" March 24th.
					0.5	Intra-abd.	645	?	" March 3d–4th (seven days).
	5 " 3 "	5th	May 1, 1897	9	0.5	" "	505	?	" May 13th (thirteen days).
" III.	4 " 7 "	5th	Aug. 26, 1897	9	0.5	Subcut.	533	400	" October 17th–18th.
					0.5	Intra-abd.	624	?	" September 2d–3d (seven days).
	9 " 27 "	8th	Feb. 15, 1898	17	0.5	" "	581	468	" March 2d (fifteen days).
" IV.	4 " 3 "	5th	Aug. 26, 1897	9	0.5	Subcut.	635	400	" October 6th–7th.
					0.5	Intra-abd.	533	?	" September 4th–5th nine days).
" V.	4 " 3 "	5th	Aug. 26, 1897	9	0.5	Subcut.	504	336	" October 5th.
					0.5	Intra-abd.	490	...	" September 5th–6th (ten days).
" VI.	2 " 18 "	3d	Mar. 15, 1898	13	0.5[1]	Subcut.	406	...	" May 2d–3d.
					0.5[1]	Intra-abd.	423	...	" April 7th (twenty-three days).
Nasua	19 " 22 "	18th	Mar. 20, 1896	16	0.75	Subcut.	455	?	" April 26th, probably chronic kidney
					0.3	Intra-abd.	405	?	" May 1st (forty-one days). [disease.
Swine I	2 " 6 "	14th	July 14, 1896	12	0.5	Subcut.	525	?	" August 7th.
					1.0	Intra-abd.	525	...	" July 25th–26th.
	11 " 23 "	16th	May 1, 1897	13	0.5	" "	450	300	" May 15th (fourteen days).
Horse I.	5 " 4 "	6th	July 24, 1897	18	0.5	Subcut.	395	...	" August 19th–20th.
					0.75	Intra-abd.	415	290	" August 7th (fourteen days).
Cat I.	4 " 15 "	5th	July 24, 1897	18	0.75	Subcut.	424	290	" August 28th–29th.
					0.5	Intra-abd.	427	?	" August 8th (fifteen days).

[1] Dilution one-third to one-fourth of that hitherto used.

Rabbits. The inoculation into the anterior chamber of the eye has been the most widely practised method. This seems to have been followed by variable results, whether due to the number of bacilli injected, the source of the bacilli, or the amount of injury inflicted on the eye.

Koch injected tubercle bacilli from various sources into the ear-vein. The bacilli were suspended in blood-serum and the suspension passed through fine gauze to eliminate coarser particles. Four rabbits were inoculated in this way with bacilli from a monkey, three with bacilli from a case of phthisis, and three with bacilli from cattle. The rabbits all succumbed in from eighteen to thirty-one days, excepting one, which was killed on the thirty-eighth day. In another experiment a culture from a case of lupus and one from a monkey were tested on rabbits. Death ensued in two to three weeks. The weight of the rabbits and the density of the suspension used are not given, so that comparisons are impossible. Moreover, the medium used (liquid serum) may not be entirely indifferent. Straus[1] mentions the slight effect produced upon rabbits by cultures of human tubercle bacilli.

In the present work the injection of tubercle bacilli into an ear-vein was used at first tentatively, then, when sharp distinctions between bovine and human cultures were made manifest by this procedure, it was continued.

Rabbits weighing from 1300 to 2200 grammes were employed. The suspension was prepared as already described, and for most of the primary tests 0.5 c.c. was injected. By referring to Table III. it will be seen that for the primary test of the last pair of cultures, Bovine VI. and Sputum VII., the suspensions were one-third to one-fourth as dense and the dose was doubled. The other cultures of which larger doses were injected are Sputum I., Nasua, and Cat I. (0.75 c.c.), and Swine I. (1 c.c.). More recent tests indicate, however, that any variation in the dose as slight as these has but little influence in modifying the duration of the disease.

As far as practicable the tests were made as soon as the purity of the cultures was beyond doubt, in order to reduce to a minimum the factor of artificial attenuation. This seems to have been on the whole inconsiderable.[2] An effort was also made to test the cultures in groups as far as possible, in order to furnish identical conditions. These groups are Bovine I. and Nasua Sputum II. and Bovine II., Sputum III. and IV., Sputum I. and IV., Horse I. and Cat I., Sputum V., VI., and Bovine III., IV., and V. Sputum VII. and Bovine VI. may be considered a group, though the inoculations were not

[1] La tuberculose et son bacille, p. 377.

[2] See Table III., Bovine Culture I.

made simultaneously, owing to an accident. The ages of the different groups of cultures varied from a minimum of nine to a maximum of twenty-four days. The total age of the cultures likewise varied at the date of the first test from one month and ten days to nineteen months and twenty-five days. These differences, which were largely counterbalanced by the group inoculations, cannot be dwelt upon here, as the table contains all the information needed for the reader to form his own opinion. It should be stated, however, that the heaviest rabbits of any group were chosen for the bovine cultures. After the inoculation the rabbits were handled very little, in order that the conditions might remain as uniform as possible. For this reason I have no temperature records, but hope to obtain them from a special series of experiments.

The results may be classed as gross or those manifest on ordinary observation and those deducible from a microscopical examination of the diseased tissue and organs. The gross results show a sharp line of demarcation between the bovine and the human cultures. While all the rabbits inoculated with the former succumbed in from seventeen to twenty-one days, of the rabbits inoculated with the latter only one succumbed in thirty-five days. The others were chloroformed after periods ranging from one month and twenty-four days to three months and eighteen days. At the time they were killed all but one had increased in weight; some but little, others much.

The rabbits inoculated with bovine bacilli manifested in most cases more or less dyspnœa at the end of eight or ten days. The lesions were practically the same in all, with slight minor modifications. The lungs, as the first and chief recipients of the injected bacilli, were in a state of expansion, which in some cases was extreme. All lobes were densely sprinkled over with small grayish tubercles, varying from mere specks to those 1 mm. in diameter. The liver was usually mottled, indicating fatty changes, and in about half the cases it was permeated with barely visible grayish points. The spleen was enlarged to two or three times its normal size and, as a rule, permeated with minute tubercles. In the kidneys the visible tubercles were scarce. In three cases they were seen in the heart-muscle; in several in the follicles composing Peyer's patch at the ileo-cæcal valve.

The sputum rabbits, with one exception, behaved quite differently from the bovine cases. A certain number showed signs of illness after seven or more days. They were quiet, somewhat drowsy, and ate little, but manifested no dyspnœa. This condition lasted one or two weeks, after which recovery took place. A certain number did not show this transitory depression. It is probable that with all, during the first month, there was loss of weight, for subsequent weighings showed no gain upon the initial weight. At the time they were chloroformed all but one had more than recovered in

weight. The lesions in these rabbits were in many respects quite different from those of the bovine rabbits. The rabbit which received the culture marked Sputum I. did not show any recognizable lesions. The difficulty experienced in the attempts to cultivate this bacillus leaves the interpretation of this case somewhat doubtful, although the microscopic preparation from the feeble culture used showed well-stained bacilli. The lesions of the other cases were quite uniform in character.

In all, the lungs contained tuberculous foci sprinkled over the various surfaces from 1 mm. to 1 cm. apart. They did not seem to interfere functionally, for the lungs collapsed normally when the thorax was opened. The tubercles frequently projected somewhat above the surface in the collapsed state of the organ. In the fresh condition the foci were observed as minute dots barely visible, owing to their translucency, as larger foci, 2 mm., in rare cases 3 to 4 mm. in diameter, also translucent excepting the centre, which was occupied by a minute opaque point, and as more diffuse infiltrations of a translucent appearance mainly at the sharp lateral margin of the lobes. These different forms of lesions were usually found associated in the same organ, the largest in the animals kept alive the longest. Necrosis was an inconspicuous feature, whereas the translucency was often so perfect as to conceal the small lesions from the eye. When placed in alcohol these became opaque and visible.

The liver usually contained minute tubercles scattered sparsely over the organ. The spleen, only very slightly larger than normal, was affected to nearly the same degree. The kidneys came next to the lungs in the extent of the lesions. Sprinkled sparingly over the cortex were opaque whitish foci from 1 mm. to 2 mm. in diameter. When the organ was incised these round foci in many cases corresponded to radial whitish lines and bands, extending from the periphery toward the pelvis, and usually stopping within the medullary portion near its base. More rarely small whitish foci were observed in the walls of the stomach or the large intestine. The lymph nodes were free excepting in one case in which the node associated with a tuberculous kidney was involved.

In all cases inspection of the affected organs revealed no degenerative changes. They were evidently not disturbed by the focal lesions, an observation strengthened by the increased weight of the animals when sacrificed. The single rabbit which died thirty-five days after inoculation had received Sputum Culture IV. It is worth while to note as a highly probable explanation of this one exception that the rabbit, after inoculation, escaped from the basket in which it was being carried and had to be chased for a long time in the animal-room before it could be penned. I at once anticipated some modification of the disease, owing to the different distribution the bacilli would undergo under the influence of muscular exertion. This anticipation was realized. The rabbit, after a week, became quiet and remained dull and drowsy without any change in respiration. On the day before death it sat in a crouching position, the hind feet drawn forward

under the body, the eyes partly closed. After death its weight was 922 grammes, the initial weight having been 1620 grammes. During the latter weeks a purulent ophthalmia developed in the left eye, and shortly before death there was a slight discharge and beginning opacity of the cornea in the right eye.

In the liver, lungs, and kidneys there were minute translucent tubercles, scarce in the lungs and kidneys, more abundant in the liver. The lesions, found in sections of hardened tissue to be relatively very immature, could not explain the rapid emaciation and death, as they were less extensive than those of the surviving rabbits, unless we assume that the different, more general distribution caused a more rapid breaking up of the bacilli and diffusion of the toxins. Another hypothesis would be the presence of foci in the central nervous system, which was not examined. A second trial upon a rabbit two months later, with conditions as nearly the same as possible, proved no exception to the general rule. The rabbit showed but little disturbance, and was chloroformed after two months and nine days. The lesions found were like those induced by the other sputum bacilli.

In order to probe still further this difference between bovine and human bacilli the lungs of all but a few rabbits were subjected to a microscopical study. Here the foci may all be considered primary and produced under like conditions. The lesions as defined in fixed and hardened tissue by the microscope in the bovine cases were characterized by rapid necrosis of the tubercle and the presence of very large numbers of tubercle bacilli. This necrosis was evident in the fresh organs from the marked opacity of the comparatively young tubercles. The tubercle itself at the stage in which it came under observation varied slightly from case to case. It consisted of a necrotic centre, absent only in the smallest foci, outside of which a zone of epithelioid cells was distinguishable. This zone was in several cases bounded by a peripheral one of cells having deeply stained nuclei and probably lymphoid. These latter cells were also intermingled with the epithelioid ones. The central necrosis appeared in two forms: it either was characterized by the presence of a very dense, deeply stained mass of nuclear fragments, or else these were present only to a slight degree, and the centre had a more rarefied aspect. In the latter case it was evident that the necrotic mass consisted of the bodies of epithelioid cells and the few nuclei present. In the former the source of the great mass of nuclear detritus remains in doubt. These dense nuclear masses were present in abundance in Bovines I. and III. In Bovines II. and IV. they were not quite so conspicuous; in Bovine V. least so. It is worthy to note here that Bovines I. and III. are the two cultures which proved rapidly fatal to cattle inoculated with them, as will be shown further on.

In the series of rabbits inoculated with human bacilli the lungs present quite different conditions. These lesions evidently develop very slowly, for in the one rabbit which succumbed after thirty-five days the tubercles were very small, translucent, the bulk microscopic in size. With the continued

life of the rabbit they grow larger. The microscopic picture differs from that of the bovine series in the rarity of necrosis and in the comparative scarcity of tubercle bacilli. The tubercles consist of aggregations of large epithelioid elements which only in the centre of the largest foci show necrosis. These epethelioid foci may be rarely enclosed by a zone of round cells. Giant cells are present, but, as a rule, in very small numbers. In the Sputum III. rabbit they were exceptionally numerous and very large. The contiguous alveoli may be occluded with patches of epithelioid cells not to be confounded with desquamated epithelium.[1] Tubercle bacilli are found only in the necrotic centres, either in very small numbers or more abundantly. In some cases they stain feebly. In all cases they are somewhat longer than the bovine bacilli in the same situation.

In addition to the foregoing inoculation tests, made as far as practicable with equal doses, a few others were tried under slightly modified conditions. A large rabbit (No. 20), weighing 2448 grammes, received into the abdominal cavity the usual dose, 0.5 c.c. of the standard suspension. Death ensued twenty-six days later. The walls of the abdomen and of the large intestine were densely studded with minute tubercles, the liver permeated with them. The lungs also were densely beset and penetrated with minute translucent tubercles. They did not differ appreciably from the lungs after intravenous inoculation. This mode of inoculation thus proved almost as promptly fatal as the intravenous injection. The same suspension of tubercle bacilli used upon the preceding rabbit was diluted with nine volumes of bouillon, and 0.5 c.c. injected into the ear-vein of a rabbit (No. 27) weighing 1892 grammes. The rabbit thus received one-tenth the usual dose. In this animal the symptoms and duration of the disease and the lesions were nearly the same as those of the rabbits inoculated with the horse-culture, to be described later. The rabbit showed evidences of disease after two weeks, with slowly increasing dyspnœa. On the thirty-fourth day it was chloroformed, as it would probably have lived but one or two days longer. The extreme relative virulence of the bovine bacilli is thus put into a clear light.

A similar experiment was made with Sputum Culture III. One rabbit received an equivalent of the usual dose, another one-tenth of this on March 1st. Both are still alive (August 19th) and the initial weights of 1707 and 1672 grammes are now 1558 and 1986 grammes respectively.

It has already been stated that the Nasua culture, presumably derived from sputum, produced neither symptoms nor visible lesions in a rabbit. The swine and the cat-culture, however, produced lesions practically identical with those due to the bovine culture.

The horse-culture takes a position midway between bovine and human cultures so far as the rabbit inoculations show. These, therefore, deserve

[1] The lesions in rabbits due to sputum bacilli resemble in many respects those produced by Prudden with boiled and washed tubercle bacilli in the same species, if we exclude the slight progressive tendency of the disease due to the living forms. See New York Medical Journal, 1891, i. 637.

a more detailed description. The first rabbit, treated like all the rest, remained apparently unaffected for a month, although the weight had fallen slightly, from 1505 to 1477 grammes. In the second month respiration became somewhat slower, and grew gradually more and more labored, so that the animal had to be chloroformed just two months after inoculation. The weight had fallen to 1232 grammes. The lesions were macroscopically unlike those in any other rabbit of the series. In the first place, the lungs failed to collapse even slightly. They are densely beset and permeated with tubercles of a grayish, feebly translucent appearance, the majority about 1.5 to 2 mm. in diameter, coalescing into patches 4 and more mm. in diameter. Minute tubercles are also visible among the larger ones. The latter may have a minute, opaque, necrotic centre. The liver is apparently free from tubercles, but the slightly enlarged spleen is beset with sharply outlined, slightly projecting grayish tubercles 1 mm. in diameter. The kidneys are affected in a manner similar to those of the sputum rabbits, but the foci are larger. There are scattering tubercles in the walls of the small and large intestines, but none in the walls of the stomach. A second rabbit, inoculated six months later, was chloroformed after forty days, on account of severe dyspnœa. The course of the disease and the lesions were like those of the first rabbit.

A noteworthy peculiarity of these cases is the presence of tuberculous foci 2 to 4 mm. in diameter in the superficial axillary and popliteal lymph nodes. These were not seen in any of the sputum rabbits, but were produced by retarding the bovine disease in a rabbit. The intermediate position of this horse-culture is well illustrated by this experiment, referred to above, in which a dilution of bovine tubercle bacilli, equivalent to one-tenth of the usual density employed, produced manifestly the same effect upon rabbits as the horse-culture. In other words, the pathogenic power of the bovine culture as measured upon rabbits was ten times that of the horse-bacilli. Further trials will, perhaps, enable us to give a rough arithmetical ratio between the pathogenic power of the bovine and the sputum-culture as affecting adult rabbits. I do not, however, consider the difference between these races to be solely quantitative.

A comparison of the lesions produced by these three races was attempted by a histological examination of the lungs, spleen, liver, and kidneys of three rabbits:

No. 16. Wt. 1527–1617.	Sputum V.	Chloroformed 3 months 7 days after inoculation.	
No. 14. Wt. 1540–1232.	Horse I.	" 2 " 4 "	" "
No. 19. Wt. 1443.	Bovine V.	Died 20 days after inoculation.	

I refrain from giving the detailed account of the lesions in each organ, and limit myself to the following summary:

Sputum V. Homogeneous epithelioid-cell foci of small size, with very little central necrosis and very few tubercle bacilli. In the lungs and kidneys these foci have lymphoid-cell mantles; in the liver well-defined connective-tissue capsules.

Horse I. Large foci in lungs, where they are so numerous as to coalesce; some large foci in kidneys; smaller ones in the spleen. In the liver the foci are represented simply by one or several large giant cells situated within the lobules. Foci large in subcutaneous lymph nodes and Peyer's patch. Necrosis of the foci quite extensive in all the organs excepting the lungs, where it is slight. Tubercle bacilli fairly abundant in all foci.

Bovine V. Large number of epithelioid-cell foci in lungs, liver, and spleen. In the latter epithelioid cells are also abundant throughout the pulp. Foci small in kidneys; necrosis under way in lung foci; tubercle bacilli very abundant in all foci.

Taking into consideration the time during which these lesions developed we may epitomize the observed differences as follows:

In the first rabbit very gradual development of the tubercles with suppression of the bacilli and reparative changes leading to a stationary condition of the disease. In the second rabbit continuous but not very rapid development of tubercles in the various organs. In the kidney and spleen evidences of limitation of the foci. No evidence that bacilli are repressed. In the third rabbit very rapid appearance of the foci with unchecked multiplication of the bacilli and rapid onset of necrotic changes.

As a matter of some interest, there may be briefly mentioned certain lesions of the eye in three of the sputum rabbits. In rabbit No. 7, inoculated with Sputum Culture IV., which animal was the only one of all the sputum rabbits to succumb (in thirty-five days), a purulent ophthalmia appeared in the left eye some time before death. Soon after a slight cloudiness of the cornea of the other eye was noticed. A discharge had started in this shortly before death. I did not associate these lesions directly with tuberculosis, although later cases make it probable that the purulent discharge was secondary to tuberculosis of other parts of the eye. At the autopsy I examined the discharge for tubercle bacilli, but found no acid-resisting bacilli

The second rabbit (No. 12), inoculated with a culture from the same source, first called my attention to this localization of the tubercle bacilli. In this animal there was noticed, some weeks after the inoculation, a slight nodular thickening of both lids of the right eye, which slowly grew more conspicuous. Vision became impaired by the enlargement and gumming together of the lids, so that the rabbit used the other eye only. When this animal was chloroformed three flattish, disk-like, firm excrescences were found on the sclera at the margin of the cornea, about 90° apart. Of these, as well as of the nodulated lower eyelid, sections were made, and both lesions proved to be tuberculous. In both the tubercle bacilli were sparingly present. The neoplasm in the eyeball had involved nearly the whole thickness of the sclera. In the eyelid the multiple foci were external to the lobules of the Meibomian glands. In still another animal eye-lesions were found. About two and one-half months after rabbit No. 16 had been inoculated with Sputum Culture V. the lids of the left eye were observed to be gummed together. A pasty yellowish exudate was found under the lids, and the cornea was slightly opaque. About three weeks later the animal was

chloroformed, and faint whitish spots were seen in both eyes, presumably on the iris. Sections of the eye hardened, unopened, in Zenker's fluid, confirmed this supposition. Small epithelioid tubercles were found in the vascular stroma of the iris as well as in one ciliary body. Linear infiltration of the cornea was observed, starting from the most affected side and extending to the middle of the cornea. In its course several sections of vessels were found. A similar infiltration had begun from the opposite side. In the foci tubercle bacilli were very scarce. The infection probably came through the blood, as infection from the point of injection on the ear is hardly supposable, since the lesions here are of the slightest character. The animals had been kept separated, and could not have acquired the infection from the exterior. The eye of the rabbit thus seems to be a very vulnerable organ, and earlier experimenters have, in a way, chosen by accident that organ in this species most likely to give positive results.[1]

The divergences noticed when rabbits weighing between 1300 and 2200 grammes are inoculated in an ear-vein with 0.5 c.c. of a well-clouded suspension of tubercle bacilli in bouillon are as follows:

1. Death of the bovine cases in seventeen to twenty-one days.

2. Rapid evolution and necrosis of the pulmonary tubercles, with very great increase of the tubercle bacilli in them.

3. Death of the sputum rabbits (one explainable exception) did not ensue, but after one and one-half to three and one-half months their original weight had been more or less exceeded.

4. The pulmonary tubercles in the sputum rabbit developed very slowly, with very little tendency toward necrosis. The bacilli were present in very small numbers only.

5. The swine and cat-cultures are to be classed with the bovine; the horse-culture stands intermediate.

Gray Mice. White mice have been pronounced quite insusceptible by Koch. Of five inoculated subcutaneously with a culture from the monkey, and twelve with a culture from miliary tuberculosis, only one of the first set showed a few grayish nodules in the lungs. On the other hand, field mice were found quite susceptible.

Two parallel tests were made upon gray house mice with cultures of Bovine V. and Sputum VI. At the time control-inoculations of the suspensions used were not made upon guinea-pigs, and subsequent developments made it doubtful whether Bovine V. was alive. This part of the experiment is therefore omitted from the table given below, and a later experiment with Bovine VI. substituted. The suspension used in this latter test was employed simultaneously upon two guinea pigs and a rabbit with the usual success.

[1] The eyes of rabbits Nos. 28 and 29 became similarly involved (see Table III.).

TABLE III.—RABBITS.

Culture.	Total age of artificial culture.	No. of transfer.	Date of inoculation.	Age of culture in days.	Dose in c.c.	Mode of inoculation.	Designation of rabbit.	Initial weight in grammes.	Final weight.	Chloroformed after	Died in
Sputum I.	10 mos. 27 days.	2d	June 16, 1897	61	0.75	Ear vein	17	1470	1681	2 mos. 3 days.	
" II.	3 " 3 "	5th	Feb. 24, 1897	24	0.5	" "	6	1380	1645	1 mo. 26 "	
" III.	1 " 19 "	2d	Apr. 3, 1897	18	0.5	" "	8	1790	1830	2 mos. 8 "	
	13 " 17 "	.....	Mar. 1, 1898	16	1.0[1]	" "	28	1707	.....	Alive Aug. 19, weighs 1558.	
	13 " 17 "	.....	Mar. 1, 1898	16	1.0[2]	" "	26	1672	.....	Alive Aug. 19, weighs 1986.	
" IV.	1 " 18 "	2d	Apr. 3, 1897	18	0.5	" "	7	1620	922	.....	1 month 5 days.
	4 " 0 "	5th	June 16, 1897	12	0.5	" "	12	1620	1722	2 mos. 9 days.	
" V.	1 " 19 "	3d	Aug. 26, 1897	10	0.5	" "	16	1517	1617	3 " 7 "	
" VI.	1 " 12 "	3d	Aug. 26, 1897	10	0.5	" "	18	1305	2061	3 " 18 "	
" VII.	1 " 10 "	2d	Mar. 1, 1898	16	1.0[3]	" "	29	1882	1788	3 " 8 "	
Bovine I.	15 " 19 "	14th	Mar. 20, 1896	16	0.5	" "	3	2279	.....	.....	17 days.
	37 " 24 "	38th	Jan. 25, 1898	12	0.5	" "	24	1795	.....	.....	22 "
" II.	2 " 27 "	3d	Feb. 24, 1897	24	0.5	" "	5	1360	.....	.....	17 "
" III.	4 " 7 "	5th	Aug. 26, 1897	10	0.5	" "	15	1775	.....	.....	21 "
" IV.	4 " 3 "	5th	Aug. 26, 1897	10	0.5	" "	17	1607	.....	.....	15 "
	9 " 23 "	9th	Feb. 15, 1897	17	0.5	Abdomen	20	2048	.....	.....	26 "
	9 " 23 "	9th	Feb. 15, 1897	17	0.5[4]	Ear vein.	27	1982	1416	.....	Killed on 34th day, very severe dyspnœa, probably within 24 hours of time of death.
" V.	4 " 3 "	5th	Aug. 26, 1897	10	0.5	" "	19	1443	.....	.....	20 days.
" VI.	2 " 18 "	3d	Mar. 15, 1898	13	1.0[3]	" "	21	2353	1877	.....	Chloroformed twenty-second [day; dying.
Nasua	19 " 25 "	18th	Mar. 20, 1896	16	0.5	" "	2	1800	Fat condition, wt.	1 mo. 24 days.	
Swine I.	2 " 6 "	4th	July 14, 1896	12	1.0	" "	1	2000(?)	.....	.....	17 days.
Horse I.	5 " 4 "	6th	July 24, 1897	18	0.5	" "	14	1540	1232	2 mos. 4 days.	
	11 " 5 "	11th	Jan. 25, 1898	12	0.5	" "	25	1658	.....	1 mo. 9 "	
Cat I.	10 " 17 "	5th	Jan. 25, 1898	18	0.75	" "	13	1320	.....	.....	20 days.

[1] Dilution about one-half of the standard.
[2] Dilution about one-twentieth of the standard.
[3] Dilution about one-fourth of the standard.
[4] Dilution about one-tenth of the standard.

In the first bovine test the four mice inoculated (two subcutaneously and two into the abdomen) all died, the first on the eighth and the last on the thirty-seventh day, without any lesions recognizable with the naked eye. In case of the four mice inoculated with the sputum culture death ensued between the eighth and the fortieth day. In one of these the lungs contained a number of whitish, rather firm nodules, 1 to 2 mm. in diameter. In sections, these were found to consist of completely necrotic foci, enveloped by a dense, broad zone of pneumonic infiltration, within which all alveoli were filled with nuclear débris. A striking feature were the immense numbers of rather slender, mainly beaded tubercle bacilli, which occupied not only the necrotic centre, but in equal abundance the pneumonic periphery. This case proved the vitality of the sputum culture, and the test is, therefore, inserted in the table below.

TABLE IV.—GRAY MICE.

Designation of culture.	Total age of culture.	No. of transfer.	Age of culture used.	Dose and mode of injection.	Results.
Sputum VI	5 months 27 days.	6th	24 days	Mouse 1, 0.5 c.c. subcut.	Dies in 34 days; no tuberculosis.
" "	.....	.....	.....	" 2, 0.5 c.c. "	Dies in 40 days; no tuberculosis.
" "	.....	.....	.....	" 3, 0.25 c.c. abdom.	Dies in 8 days; no tuberculosis.
" "	.....	.....	.....	" 4, 0.25 c.c. "	Dies in 34 days; tubercles in lungs.
Bovine VI.	2 months 18 days.	3d	13 days	" 5, 0.25 c.c. subcut.	Chloroformed in 37 days.
" "	.....	.....	.....	" 6, 0.25 c.c. "	" " "
" "	.....	.....	.....	" 7, 0.25 c.c. abdom.	Dies in 5 days.
" "	.....	.....	.....	" 8, 0.25 c.c. "	" "

The second bovine test resulted in the death of the two mice receiving the dose into the abdomen in five days. There were no lesions recognizable. The two mice inoculated subsequently were active up to the thirty-seventh day, when they were chloroformed. Lesions were not found.

Pigeons. Fowls and pigeons have been used with success in distinguishing avian from mammalian tubercle bacilli. Hence it was thought best to test human and bovine bacilli on pigeons. The cultures used are given below in the table. The bacilli, in the form of bouillon suspensions, were injected into the pleuro-peritoneal cavity, the needle being introduced caudad of the sternum. In one case the injection was made into the wing-vein. The inoculations were, in general, negative, with the possible exception of that of the swine culture. In this bird there was found hyperæmia of the serosa of the intestines, with an eruption of scattering minute grayish dots. There

were similar opaque points on the air-sac membranes. On the duodenal loop were found some particles of viscid exudate, composed exclusively of coarsely granular cells. In this exudate some tubercle bacilli were still recognized by the specific stain. In some of the other pigeons there were a few opacities of the mesenteries and air-sac membranes, with perhaps one or more conspicuous Peyer's patches. Even in refractory animals lesions, such as these, might be anticipated where the tubercle bacilli are deposited.

TABLE V.—PIGEONS.

Designation of culture.	Total age of culture.	No. of transfer.	Age of culture used.	Designation of pigeon.	Dose and mode of injection.	Remarks.
Sputum II.	6 months 14 days.	9th	11 days.	No. 2	1 c.c. abdomen.	Chloroformed in 45 days; negative.
" III.	3 months 19 days.	5th	11 "	" 4	1 c.c. "	Chloroformed in 57 days; negative.
Bovine II.	5 months 26 days.	9th	11 "	" 1	1 c.c. "	Chloroformed in 49 days; negative.
Swine I.	1 year 19 days.	17th	11 "	" 8	1 c.c. "	Chloroformed in 57 days; minute excrescences on portions of intestine and membranes of air-sacs.
Sputum V.	5 months.	5th	31 "	" 5	¾ c.c. wing vein.	Chloroformed in 47 days; negative.
Bovine V.	8 months 14 days.	8th	24 "	" 8	1.5 c.c. abdomen.	Chloroformed in 49 days; negative.
Horse I.	11 months 5 days.	11th	12 "	" 7	0.5 c.c. "	Chloroformed in 50 days; negative.

Cattle. It is a noteworthy fact that, in spite of the great economic, agricultural, and hygienic interests involved in the diffusion of bovine tuberculosis throughout the world, no experiments upon cattle with cultures of the bovine bacillus had been made up to the time of my first experiments, published in the TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS for 1896. Experiments upon cattle with the human bacillus had been made by several observers. A discussion of these tests I shall defer to the end of this article, because of certain secondary questions which will be clearer when my tests have been described.

The results of the inoculation of two heifers into the lungs with Bovine Culture I. and *Nasua* culture have already been published.[1] It may be stated briefly that the bovine culture produced general

[1] Loc. cit.

tuberculosis, ending fatally in thirty-five days, while the Nasua (human) culture failed to produce any recognizable lesions.

During the warm season of 1897 inoculations were made with five sputum, one swine, and four bovine cultures upon as many cattle. For these ten animals I am indebted to the Massachusetts Board of Cattle Commissioners, who have shown much interest in the progress of these investigations because of the need felt by them of more definite information upon the relation of bovine tuberculosis to the human disease. The test was carried out in two series, the first including four, the second six animals. The culture material used was suspended in bouillon, as described, the density of the suspension being about the same as that of a typhoid culture in bouillon twenty-four hours old. In both series the dose was 2 c.c. of such a suspension.

SERIES I. The four animals of this series were inoculated with the following cultures:

Sputum	II.	Total age	5	months	9	days;	8th	transfer.
"	III.	"	2	"	15	" ;	4th	"
Bovine	II.	"	5	"	2	" ;	5th	"
Swine	I.	"	11	"	23	" ;	16th	"

The swine culture is probably bovine in origin, and it was used on this supposition. Assuming that tubercle bacilli become slowly weakened in virulence by artificial cultivation, we should endeavor to use cultures as fresh and of as nearly the same age as possible. This theoretical demand cannot be successfully met, because of the many difficulties surrounding such work. Of the four cultures used, Sputum II. and Bovine II. are of nearly the same age, while Sputum III. is but half as old as they, and Swine I. more than twice as old.

In making the injection the space between the sixth and seventh rib was chosen. The needle was inserted about three inches above the level of the elbow (olecranon process). It was found subsequently at the autopsy that the point chosen was too low, and that in all of the animals the needle, leaving the lungs intact, pierced the diaphragm. Some of the bacilli were discharged into the muscles of the thoracic wall, some into the abdominal cavity, and some into the pleural cavity. Bearing this accident in mind, we may now go to a description of the further history of the inoculated cattle. They were all housed in a spacious, well-ventilated barn, in large, commodious horse-stalls. A piece of ground adjoining the barn was enclosed, and in this the animals spent six to seven hours a day for about four weeks. Thereafter the animals were separated into two lots, one lot being out several hours in the morning, the other several hours in the afternoon. The two which received the bovine and the swine culture were allowed to run together,

similarly the two which received the sputum cultures. It might be claimed that there was in this arrangement a possible danger of transmitting the bacilli from one animal to another and of infecting the ground. There was no evidence of this at the post-mortem examination, and the arrangement was considered safe at the start, because it takes some time for the tuberculous tissue to become disintegrated. It was, however, deemed prudent not to keep the animals longer than two months, on account of the imperfect isolation.

In apportioning the cultures to the animals the sputum cultures were injected into the youngest animals, in order that these cultures might have any advantage likely to accrue from difference in age. Two yearlings (without any permanent incisor teeth) received the two sputum cultures; the bovine culture was injected into a heifer about two and a half years old; the swine culture into a heifer about two years old.

They were killed and examined at the Brighton (Boston) abattoirs, with the co-operation of the Board of Cattle Commissioners, just two months after the day of the injection. Before injection, these animals had been tested with tuberculin by the Board and found free from tuberculosis. Still, since this agent occasionally allows an animal to escape which contains foci of the disease, attention was directed to this point at the autopsies. No lesion, however, was found which from its situation and appearance could be referred to any former spontaneous infection.

Let us examine first the effect of Sputum Culture II. and Bovine Culture II., which were of nearly the same age when injected.

The weight of the yearling which had received the sputum culture had risen in the two months from 520 to 580 pounds, that of the heifer from 650 to 710 pounds. There was no continuous fever recognized in either animal, though the temperature was taken twice a day—morning and afternoon. The fluctuations noticed were evidently due to the effect of the sun while the animals were in the enclosure.

The lesions in the yearling were very slight. At the seat of inoculation, between the sixth and seventh ribs, a mass of tubercles attached to pleura about one by one-half inch in dimension, the tubercles composing it partly cheesy, partly firm. Near the cephalic border of ventral lobe of right lung a subpleural nodule, not yet necrotic, about one-eighth inch in diameter. On abdominal aspect of diaphragm, right side, about twenty-four isolated tubercles, one-twelfth to one-eighth inch in diameter. A few similar tubercles on the omentum, which is slightly adherent to the large intestine. When adhesion was removed, about six or seven nodules found on cæcum, one-twelfth inch in diameter. Evidently the injection needle had passed through the diaphragm into abdomen, deposited some fluid there and some in thorax when partly withdrawn.

The lesions in the heifer which had received the bovine culture were quite extensive, and were diffused through thorax and abdomen, owing to the penetration of the diaphragm by the needle of the injection syringe.

Thorax. The right pleural cavity shows an abundant eruption of tubercles along the borders of the ribs. Some of the masses formed are characteristically flattish, grape-like, and in bulk quite large. One mass measured eight and one-half by three by one and one-half inches. Others of similar dimensions were present. On the lateral margin of the right lung a series of loosely-attached, flattish neoplasms, up to two inches in diameter, besides hyperæmic fringes of loose connective tissue. On the convex surface of this lung only a few tubercles. Large patches of tubercles on pericardium and diaphragm.

In the muscular portion of diaphragm, right side, a mass of tuberculous tissue (probably place where needle penetrated), one and one-half by one and one-half by one-half inch in dimensions. The caudal of the series of dorsal mediastinal glands about twice normal size, on account of the presence of many small foci, showing in some cases an opaque, yellowish centre.

Abdomen. The omentum densely studded with agglomerations of tubercles, covering the greater part of its surface. These masses vary up to one-half inch in thickness. Similar patches on abdominal aspect of diaphragm and on spleen. Fewer patches on gall-bladder and on liver. In one of the portal glands a one-fourth-inch focus, pale, grayish, permeated with small calcareous spicules.

The examination of sections of the pleural eruptions and of one of the dorsal mediastinal glands showed the typical lesions of bovine tuberculosis, with its foci of epithelioid cells and its numerous giant cells containing a few tubercle bacilli. Any detailed description of these lesions would be simply a repetition of familiar facts.

We have in these cases a wide divergence in the result of inoculation. The human bacillus produced a slight eruption of small tubercle-like bodies, which did not present even microscopically the characters of true tubercles, while the bovine bacillus produced an exquisite case of pearly disease, both in thorax and abdomen, with the formation of large grape-like masses in the chest.

The youngest sputum culture (III.) was injected into a yearling weighing 410 pounds. At the end of two months the weight had risen to 480 pounds. The lesions found are slight.

On the abdominal aspect of diaphragm, right side, a patch of isolated tubercles about two inches in diameter, the tubercles themselves about one-sixth inch in diameter and about one-half inch apart. They are grayish, opaque. At place of inoculation, on serous aspect of ribs, a flattish neoplasm, one inch in diameter and about one-eighth inch thick. Other lesions not detected. In this case also the needle evidently entered the abdomen through diaphragm. Sections made from the small isolated tubercles on the abdominal surface of the diaghragm show them to be masses of newly forming tissue. They consist in the main of spindle shaped connective-tissue cells running in parallel and interlacing groups and richly supplied with vessels. No trace of the characteristic tubercle formation or of bacilli, although these bodies are evidently due to the bacilli injected.

The swine-culture was injected into a somewhat older animal, weighing 620 pounds; after two months the weight was 660 pounds. The autopsy showed the following conditions:

At place of inoculation (right chest-wall) a subcutaneous tumor, about two inches in diameter, made up of a very dense connective-tissue sac, one-fourth inch thick, which encloses a pale-yellowish semifluid mass (caseous). There are besides this focus, in the same situation, three smaller nodules, from one-half to three-fourths inch in diameter, the largest with caseous centre. On the pleural aspect a similar one-half inch centrally softened focus.

In nearly the centre of the right half of diaphragm and projecting into the abdomen for one-half inch is a tumor representing a portion of a larger focus in the muscular portion of the diaphragm about one inch in diameter. This focus is likewise caseous, diffluent centrally. On all the ribs of right pleural cavity are eruptions of small tubercles, reaching, in some instances, a diameter of one-eighth inch. Besides the palpable tubercles there is along one border of each rib a line of vascular fringes of connective tissue. In many of these fringes the tubercles are not noticed, although the fringes themselves are evidently a result of the injection.

Along the lateral border of the right lung similar vascular fringes of tissue containing tubercles. These fringes extend dorsad for about two inches on the ventral and cephalic lobes.

Diffuse eruption of minute tubercles on pleural aspect of the diaphragm, right half.

Large caudal mediastinal gland contains large numbers of tubercles, varying in size from mere points to those one-eighth inch in diameter, and showing beginning necrosis. Left bronchial gland several times normal size. Ventral mediastinal gland several times normal size and containing several large centrally caseous foci. One mesenteric gland contains several small necrotic tubercles.

In this case many of the bacilli had been deposited in the fleshy portion of the diaphragm and some under the skin, and had thus been prevented from exerting their greatest power. Sections were made of the subcutaneous foci, the anterior mediastinal and bronchial lymph glands, and of the vascular fringes on the pleural aspect of the diaphragm. The glandular and subcutaneous lesions are characteristically tuberculous, with a greater tendency toward necrosis and disintegrations of the tubercles than in the animal inoculated with Bovine Culture II. The lesions of the serous membrane are more vascular and show greater tendency toward the formation of connective tissue around the minute tubercles. In general this culture must be considered less potent than the bovine culture. Whether this is due to the more prolonged artificial cultivation or to the species through which the bacillus had passed remains unsettled.

SERIES II. In this experiment three sputum and three bovine cultures, recently isolated, were used. The bovine cultures were of nearly the same

total age; the sputum cultures differed somewhat from them and from one another in this respect.

Sputum	IV.	Total age	6 months	10 days;	7th transfer.
"	V.	"	1 month	19 " ;	3d "
"	VI.	"	1 "	12 " ;	3d "
Bovine	III.	"	4 months	7 " ;	5th "
"	IV.	"	4 "	3 " ;	5th "
"	V.	"	4 "	3 " ;	5th "

The cultures used for the injection were all nine days old, grown on the same lot of dog's serum. Control-inoculations of guinea-pigs and rabbits will be found on Tables II. and III. The animals at my disposal, unfortunately, varied considerably in age, and, in assigning the cultures, the advantage was given to the human cultures:

Sputum IV.	Yearling,	525 lbs.;	no permanent incisor teeth.
Bovine III.	" bull,	645 lbs.;	" " "
Sputum V.	Cow,	675 lbs.;	about 4 years old.
Bovine IV.	"	850 lbs.;	" 12 " "
Sputum VI.	"	865 lbs.;	" 3½ " "
Bovine V.	"	875 lbs.;	" 6 " "

The injection of the cultures was carried out as in Series I., excepting that the point of insertion of the needle was chosen higher up, about eleven inches above the elbow of the animal when in the standing position, between the seventh and eighth ribs. The length of the needles used was about two inches. The care of the animals was the same as that bestowed on the preceding lot, excepting that the bovine and the sputum animals were kept separate in the outdoor enclosure from the start, the one lot being out in the morning, the other in the afternoon. They were kept two months, with the exception of the young bull, which died seventeen days after the inoculation. The four cows of this lot gave at the start altogether about eight quarts of milk; the secretion was slowly dried up, so that in the sixth week a very little—amounting perhaps to one quart in two days—was removed. The milking was continued chiefly to prevent any udder troubles during the experiment and to maintain normal conditions. The temperature was taken but once a day, at noon.

In comparing the temperature records of these six animals it was noticed that the three animals which received the bovine cultures had a high temperature immediately after the inoculation, which lasted until the death of the bull, and about three weeks for the remaining two animals. At the same time no such elevation of temperature was recorded for the animals receiving the three sputum cultures. There was but one well-defined rise of temperature in the case of the yearling, from the thirteenth to the sixteenth day after inoculation. The other irregularities are probably due to the fact that the temperature was usually taken after these animals had been in the enclosure in the sunshine for several hours. Those with the high temperature were kept much of the time in the cool barn in the morning, which probably

depressed the fever-curve somewhat. After the period of fever no other elevations were noted up to the close of the experiment.

The young bull, inoculated with Bovine Culture III., showed, besides the prompt onset of a high temperature, general and local disturbances about a week after the inoculation. The breathing became rapid, the appetite had partly gone; emaciation and weakness supervened. He was unable to get up September 11th, and died the following night.

The autopsy revealed a severe miliary tuberculosis of both lungs with marked congestion and œdema of the organ. Normal collapse no longer possible. The associated lymph-glands were much enlarged and infiltrated with minute tubercles. Patches of minute tubercles were found on the pleural covering of the ribs and on the omentum. Sections from the lungs, dorsal mediastinal glands, pleural neoplasms, liver, spleen, and kidneys were examined. In the lungs, mediastinal glands, and pleural neoplasms tubercles were very numerous, in the liver less abundant. In the kidney sections none were seen. In these different situations the tubercles presented nearly the same peculiar features which distinguished them readily from the tubercles of the spontaneous disease in cattle. To make the differences clearer, a brief description of the lesions in a spontaneously diseased lymph-gland may not be out of place:

A rarefied area within the follicle containing a few nuclei having the characters of endothelioid nuclei and belonging to what are generally known as epithelioid cells, which are embedded in or whose outlines are fused with a matrix appearing either homogeneous or else very delicately reticulated. In larger foci this rarefied area contains also one or more giant cells whose body is frequently seen merging by prolongations into the reticulated matrix of the tubercle. Among the epithelioid nuclei are isolated nuclei closely resembling those of lymphoid cells. Tubercle bacilli are, as a rule, scarce, and situated usually within giant cells. The larger foci are centrally necrotic, that is, they contain a coarse trabecular matrix staining with eosin and picric acid, and containing scarcely any nuclei and very little if any fragments of nuclear origin. In this mass tubercle bacilli are rarely found. In the lesions of the bull the tubercles have in the first place no giant cells. The new tissue appears to be made up of cells resembling the usual epithelioid cells of tubercle, but much more crowded together and with less definition of the cell outlines. The nuclei are mostly distorted, drawn out, band-like or horseshoe-like, and twisted into various bizarre forms. Condensation and fragmentation of the nucleus are also seen. In the tubercles in all situations, much fibrin is demonstrated by Weigert's stain. This is especially distinct in the liver tubercles. Here the intercellular substance from material hardened in alcohol stains deeply in eosin. In sections subjected to Weigert's fibrin stain this substance is blue, appearing throughout the tubercle both as a delicate mesh and as very coarse trabeculæ. In material hardened in Zenker's fluid the fibrin stain is less pronounced. In all the tubercles, large numbers of tubercle bacilli are present. These differences are probably due to the rapidity of the process.

On October 27th, the remaining five animals were killed at the Brighton abattoir with the co-operation and assistance of the Board. The three sputum animals had all gained in weight:

Yearling	(Sputum IV.)	from 525 to 610 lbs.
Cow	(" V.)	from 675 to 750 lbs.
"	(" VI.)	from 865 to 960 lbs.

Sputum Culture IV. One permanent incisor on the right has appeared since date of inoculation. In utero a fœtus about three months old. At point of inoculation in the subcutaneous tissue a small nodule about one-quarter of an inch in diameter with contents soft, cheesy. Attached to this is another smaller nodule about one-eighth of an inch in diameter.

On the right side of the chest-wall, pleural aspect, there are attached along the six caudal ribs, soft, dark-red pendulous masses of newly formed, highly vascular, connective tissue. At point of inoculation, between the seventh and eighth ribs, a flattish pediculated mass of tissue of brownish-red color. On the tenth rib another mass about three-eighths of an inch in diameter. The left side of thorax is normal.

Right lung. On the smaller (cephalic and ventral) lobes newly formed, delicate fringes of hyperæmic connective tissue which appears also along the free lateral margin as a delicate band about one-half of an inch broad, as well as on a portion of the convex surface of the lung, occupying exclusively the lines representing the boundaries of the lobules.

In the large caudal lobe which is similarly beset with the vascular fringes, a tumor, representing the place where the needle penetrated the lung tissue, projecting slightly above the convex surface, is found two inches from the caudal tip. This tumor, about three-quarters of an inch in diameter, contained a completely disintegrated mass and about a dozen surrounding foci, one-sixteenth to one-eighth of an inch in diameter, with yellow softened centres. On the margin of this same lobe, in addition to the vascular fringes, are four firm masses of grayish tissue, smooth, flattish, attached by pedicles to the margin of the lobe. The diameters of the largest are one quarter and one-half inch.

On large (caudal) lobe of left lung there is only a very little development of vascular fringes. Embedded in the same lobe near lateral margin is a uniformly grayish, slightly translucent mass, sharply defined from the enveloping normal lung tissue. Sections of this focus showed a peculiar lymphoid structure of the tumor, in the centre of which a parasite was lodged. Not having any relation to the inoculation disease, it need not be further discussed.

Attached to the cephalic lobe of the left lung by a pedicle is a small flattish, smooth mass of new tissue.

The pleural aspect of diaphragm and portions of the pericardium are covered with areas of the highly vascular neoplastic tissue; in some, small nodules can be felt at the free extremity of this tissue.

On the right ventricular surface of the heart four flattish pediculated masses about as large as split peas are attached.

The various lymph-gland systems, ventral and dorsal mediastinal and bronchial glands do not show the presence of tubercles or any augmentation in size.

Of this case, sections of the primary lung focus, of two of the pediculated bodies (one from the lung, one from the rib), and of the vascular fringes from the lateral border of the lungs were examined.

The small foci immediately bordering the disintegrated primary focus vary from 0.2 to 2 mm. in diameter. The smallest do not differ essentially from ordinary tubercles excepting in the scarcity of giant cells. The larger ones are centrally necrotic, with a marked tendency toward encapsulation on the periphery by the condensation of circularly disposed fusiform connective-tissue cells. In the smallest tubercles, bacilli are scarce, in the largest they are numerous within the necrotic centre, where they appear as slender, often bent, sometimes fragmented and rather feebly stained rods. In the surrounding epithelioid zone a few well-stained bacilli are present. Passing from the primary place of deposit the only other lesions are those of the pleura. These occur in two forms, as vascular fringes and as firm, smooth, pediculated bodies, some flattish, like pumpkin-seeds in size and outline.

The vascular fringes occur: 1, as mere endothelial tubes; 2, as such enveloped by a layer of wavy fibrillar tissue and covered with a layer of endothelial cells; and, 3, as vessels sheathed with a zone of round cells, proliferating endothelial and connective-tissue cells in addition to the fibrillar tissue. Acidophile polymorphous leucocytes are present here and there throughout the granulation tissue. Mitoses are occasionally seen. After a prolonged search through seven sections one minute rarefied area detected. In it evidently a tubercle bacillus with long axis nearly at right angles to the section.

The vascular fringes from the thoracic aspect of the diaphragm are like those from the lungs. In the former no signs of tubercle formation.

Sections from one of the neoplasms attached to the ribs show two fairly distinct regions, an outer of dense connective tissue and an inner made up of foci of lymphoid elements and a central necrotic core. This latter body was evidently a vascular offshoot of the pleura which, before necrosis, had attached to or embedded in it many lymphoid cells, for the necrotic core contains much nuclear matter traceable to such cells. This core is partly enveloped by a ring of epithelioid cells with nucleus at the outer end, like those around a foreign body. Some are multinuclear and resemble giant cells. In the zone immediately outside of this cellular ring are several characteristic giant cells. There are no tubercle bacilli nor is there any tissue recognizable as epithelioid and identifiable as tubercle.

Sputum Culture V. Cow, about four years old. In utero a fœtus three to four months old.

Development of vascular fringes along one border of ribs of the right side of thorax, as in preceding case, but amount relatively slight. In the intercostal muscles at the point of inoculation a mass of, perhaps, a dozen small grayish tubercles.

In the large caudal lobe of the right lung, in the same situation as in preceding case, a projecting tumor about one inch in diameter. When incised, it is found composed of two one-half-inch foci of disintegrated cheesy-viscid matter enclosed in thin, smooth capsules. No surrounding infiltration. Along the margin and on the caudal surface of this lobe, slight development of pendulous vascular tissue and a sessile tubercle about 4 mm. in diameter. On the left caudal lobe only very slight production of vascular tissue.

On the surface of one of the middle dorsal mediastinal glands an aggregation of minute tubercles, the whole about one-half inch in diameter. Embedded in the cortex of the same gland two minute tubercles.

In this animal the disease of the middle mediastinal gland, although very slight, is shown in sections to be tuberculosis. The lesions are not to be distinguished from those of the spontaneous disease in cattle, excepting in the presence of considerable numbers of tubercle bacilli. The tubercles themselves contain the usual number of giant cells, and the largest ones are centrally necrotic, the necrosed mass being indistinctly fibrillar in character, staining deeply with eosin and devoid of nuclear *débris*. The bacilli in this mass stain rather freely when compared with the deep stain of those in the giant cells on the periphery of the tubercle. This lesion will be again referred to in summing up the experiments.

Cow (Sputum Culture VI.). In utero a fœtus about four months old.

Within the thorax on the right side, between the seventh and eighth ribs, is a small, pediculated, blackish (hemorrhagic) mass of firm tissue about as large as a pumpkin-seed, another on the tenth rib. On most of the ribs behind the seventh are gelatinous-looking pendulous vascular fringes of neoplastic tissue. On the pleural surface of the diaphragm a similar development of vascular tissue and several firm pediculated masses like those on ribs.

Of the right lung the cephalic lobe shows very slight formation of marginal fringes. In the ventral lobe, whose tip is adherent to the pericardial fat, a uniformly grayish, sharply-defined focus, one-fourth inch in diameter.

In the same situation as in the preceding cases the caudal lobe shows a slightly projecting tumor, about one and three-fourths inches in diameter externally. When incised it is found to consist of a smooth-walled sac, one and one-fourth inches in diameter, containing a yellowish, curdy mass, together with a little turbid fluid. No surrounding infiltration. On the convex surface of this lobe there is a slight growth of vascular tissue. Near the caudal tip a flattish mass, partly yellowish, partly blackish, attached by loose tissue to the margin of the lobe. It is about one inch long and one-half inch thick.

In the abdomen, a flattish, sessile mass of pinkish-gray tissue, about three-fourths inch in its largest diameter, attached to omentum.

In this animal, sections of the grayish focus in the ventral lobe of the right lung and of the suspicious sessile mass on the omentum demonstrated the fact that both lesions are parasitic in origin, and due to the same cause

as the lung focus in cow inoculated with Sputum IV. Both foci are made up of spherical agglomerations of lymphoid cells, in the centre of which the parasite is situated.

The largest of the pendulous masses from the lungs was examined microscopically and found to be similar in structure to those already described. It consists chiefly of a connective-tissue stroma of interlacing fibres, in which are embedded many capillaries. Scattered through the inner half of the mass are quite small foci of epithelioid and lymphoid cells, but giant cells are absent. In these foci a few tubercle bacilli are found. The periphery of this pendulous mass consists of circularly-condensed connective tissue, beneath which is a homogeneous, somewhat reticulated substance, staining well with eosin and enclosing a few tubercle bacilli. It is probably a layer of fibrin undergoing hyaline degeneration. Small areas of it are still stainable with Weigert's fibrin stain.

Of the three animals receiving bovine tubercle cultures, the fate of one (young bull, No. 71) has already been given. The two other cases remained stationary in weight:

No. 88. Original weight, 850 pounds; weight at end of experiment, 850 pounds.

No. 63. Original weight, 875 pounds; weight at end of experiment, 870 pounds.

The autopsy notes are, in brief, as follows:

No. 63 (Bovine Culture V.). White cow, spotted with red. Horns sawed off. Probably six years old. Fœtus in utero about two months old.

Thorax. Right lung adherent to chest-wall in several places. At point of inoculation, between seventh and eighth ribs, an excrescence of the costal pleura, about three-fourths inch in diameter, of dense pearly-looking connective tissue, enclosing a disintegrated mass. Numerous masses and aggregations of small tubercles on all ribs. These masses in some cases are several inches in length. The left side of thoracic wall, below the level of the point of inoculation on the opposite side, is covered with a uniform, pinkish-gray deposit of very minute tubercles. Eruptions of tubercles on pleural surface of diaphragm and on pleural covering of dorsal mediastinal space.

On caudal lobe of right lung a considerable number of tubercular masses, flattish, sessile, from one-eighth to three-fourths inch in diameter. Between the cephalo-lateral border of this lobe and the pericardium is a mass of newly-formed tissue, dense, in which are embedded many minute yellow tubercles and masses of pericardial fat. The whole is about as large as a fist. It binds the lung tissue, pericardium, and diaphragm together. Many tubercles on the caudal surface of this same lobe. There is no distinct focus in this lobe as a result of the injection, and it is probable that much of the fluid was deposited in the pleural cavity. But palpation reveals throughout both lungs small, shot-like bodies in close proximity. On section, numerous yellow tubercles, from one-thirty-second to one-sixteenth inch in diameter, are found embedded in the lung tissue of all lobes.

The dorsal mediastinal lymph-glands are all several times their normal dimensions. They contain many coalescing yellow tubercles. The ventral (anterior) mediastinal glands are similarly enlarged, and the cut surface shows a uniformly cheesy parenchyma.

Minute grayish points under the capsule of the liver.

In the spleen, all Malpighian bodies converted into tubercles with yellow opaque centre. In left kidney several minute grayish tubercles.

Of this case, sections of the left lung, left costal pleura, the large caudal mediastinal gland, and of the spleen were examined.

The tubercles from the lungs do not differ from those found in spontaneous tuberculosis. The centre is, as a rule, necrotic, and contains a few tubercle bacilli. Outside of this is a zone of nuclear fragments and entire nuclei, shading off into a peripheral zone of epithelioid and lymphoid cells and cells with spindle-shaped nuclei. Giant cells are present in nearly all the tubercles. The new growth on the left side of the thorax consists essentially of newly-formed vascular fringes, in which are embedded minute tubercles with scarce bacilli and occasional giant cells.

In the caudal mediastinal gland the tubercles vary from a mere giant cell to those 2 mm. in diameter and centrally necrosed. The latter are like those in the lung tissue. The bacilli in some necrotic foci are numerous, in others few in number.

In the spleen the follicles contain epithelioid cell foci, some of which are centrally necrosed, and which contain many bacilli. Fibrin is not demonstrable is these foci.

No. 88. (Bovine Culture IV.). Red and white cow. Teeth very much worn; probably twelve years old; dehorned. Not pregnant.

No deposit in subcutis at point of inoculation. The eruptions of tubercles on the costal pleura of the right and the left side are in character very much like those of the preceding case (No. 63), but less extensive.

Right lung. Lobes adherent to pericardium. Adhesions readily severed. On convex surface of the caudal lobe of this side a considerable number of flattish sessile tubercles, from one-sixteenth to one-half inch broad. The caudal aspect of this lobe is similarly beset with them, but in less abundance. Along the margin of this lobe are loosely attached, small, elongated masses of tubercles.

At the same situation in this lobe as in the sputum cases there is a fluctuating tumor, about two inches in diameter, slightly projecting. It consists of a capsule with nearly smooth walls enclosing a soft caseous mass. It is surrounded by a zone of small necrotic tubercles, and with lobules containing numerous minute, grayish foci.

On the cephalic lobe of the right lung are a considerable number of grayish tubercles. Throughout all lobes are scattering tubercles in the lung-tissue, some very minute, others larger and opaque yellowish in color.

The pleura in the dorsal mediastinal space is beset with a large number of small tubercles; similarly the pericardium. The right half of the dia-

phragm is beset with flattened aggregations of tubercles. Between the ventral lobe of the right lung and the pericardium, and fastening them together, is a mass of newly formed connective tissue and fat enclosing numerous softened foci.

The large dorsal mediastinal lymph gland is enlarged and contains a large number of yellow tubercles. The central portion of the gland is uniformly caseous. In the left bronchial gland a small number of tubercles; in the ventral mediastinal glands a considerable number. Organs of the abdomen appear free from tuberculous changes. Of this case only the tubercles disseminated through the lungs were examined microscopically. For this purpose the left lung was chosen. The tubercles are small, compact up to 1 mm. in diameter. In structure they are indistinguishable from the spontaneous bovine tubercles. The bacilli in them are few in number, rather short, thick, and deeply stained.

A summary of the outcome of this last experiment may now be made. The points of difference between the inoculation disease produced by bovine and by human (sputum) bacilli are several.

1. The bovine cases either remained stationary in weight or lost slightly, while the sputum cases gained 75 to 85 pounds. Still the age of one of the bovine cases may be partly responsible for stationary weight.

2. There was marked fever in the bovine cases for three weeks after the inoculatiun; practically none in the sputum cases.

3. There were well-marked differences in the lesions produced. In the sputum cases the lesions are nearly the same and consist in:

a A tumor in the right caudal lobe of the lung, about one inch in diameter, projecting somewhat above the surface of the lung. This represents the place where the needle penetrated into the lung-tissue and deposited the tubercle bacilli. In each case the contents of this tumor were softened and converted into a curdy mass, enclosed in a thin-walled capsule, smooth internally. The disease was not spreading from this point, nor were tubercles visible in the lymph glands of the lungs and thorax, excepting in one gland of No. 39 (Sputum V.).

b. The free margin of the right lung and the pleural covering of the ribs on the right side were béset with a new formation of loose vascular fringes or shreds in which, in only one case, some minute nodules could be felt, and some flattish pediculated masses, which did not resemble tubercles at all histologically, or which were only abortive forms of the same.

Among the bovine cases we have the following characteristic points to note:

a. Disseminated tuberculosis of the lungs, severest and fatal in No. 71, the youngest; least pronounced in the oldest, No. 88. Associated with this a local disintegrated focus in the lungs of No. 88.

b. Tubercle deposits on lungs, pericardium, diaphragm, and the ribs, resembling closely the product of the natural disease in cattle. Extension of the eruption to the costal pleura of the left side.

c. Extensive tuberculosis of all or nearly all the lymph-glands of the thorax, including both mediastinal chains.

d. Slight tuberculosis of other organs—spleen, liver, kidneys—in two out of three cases.

A summary of the three separate tests on cattle (including the published experiment), in which twelve animals were used, shows that six animals were inoculated with human bacilli, five with bovine bacilli; one animal was inoculated with swine bacilli.

Of the sputum cases, one showed no disease, two showed very slight lesions, three showed only local lesions without dissemination.

Of the bovine cases, two died of generalized disease, two showed extensive lesions, one showed less extensive lesions.

In the swine case the lesions were less extensive than in the bovine cases.

On the Significance of Varieties among Tubercle Bacilli.

The foregoing experiments, while they show unmistakably the close relationship existing among the various cultures studied, nevertheless justify us, if only to guide and stimulate further study, in establishing a distinctively human or sputum and a bovine variety of the tubercle bacillus. It might be better to omit the host designation of such varieties in order to anticipate assumptions that they are necessarily limited to the host whose name they bear. Still the convenience of using the host's name is so great that I shall succumb to it. The characters upon which the bovine variety may be based reside, morphologically, in the invariably short, straight form and in the greater resistance of this form to modifying influence of culture-media; biologically, in a greater resistance to artificial cultivation and in a much greater pathogenic activity toward rabbits, guinea-pigs, and cattle.

TABLE VI.—CATTLE.

Designation of culture.	Total age of culture.		No. of transfer.	Age of culture used.	Amt. of suspension of bacilli injected.	Designation of animal.	Age, etc.	Original weight in pounds.	Final weight in pounds.	Date of inoculation.	Result.
	mos.	days		days							
Bovine I.	5	4	3d	10	4 c.c.	No. 284	Heifer, 2¼ years old, common stock, pregnant.	(?)	(?)	May 4, 1895	Died in thirty-five days of generalized tuberculosis.
Nasua narica	9	9	8th	10	4 c.c.	No. 300	Heifer, 2½ years old.	(?)	(?)	May 4, 1895	Killed June 27, 1895; no lesions.
Sputum II.	5	9	8th	9	2 c.c.	No. 2616	Yearling.	520	580	May 1, 1897	Killed July 1, 1897; lesions very slight.
" III.	2	15	4th	9	2 c.c.	No. 2634	Yearling.	410	480	May 1, 1897	Killed July 1, 1897; lesions very slight.
Bovine II.	5	2	5th	9	2 c.c.	No. 2635	Heifer, 2½ years old.	650	710	May 1, 1897	Killed July 1, 1897; extensive pearly disease in thorax and abdomen.
Swine I.	11	23	16th	13	2 c.c.	No. 2672	Heifer, 2 years old.	620	660	May 1, 1897	Killed July 1, 1897, well-marked pleural tuberculosis with invasion of lymph-glands.
Sputum IV.	6	10	7th	9	2 c.c.	No. 79	Yearling, about 1½ years old.	525	610	Aug. 26, 1897	Killed October 27, 1897, abscess in lungs at point of injection, new vascular tissue on ribs and lungs.
" V.	1	19	3d	9	2 c.c.	No. 39	Cow, 4 years old.	675	750	Aug. 26, 1897	Killed October 27, 1897, lesions same as preceding.
" VI.	1	12	3d	9	2 c.c.	No. 76	Cow, 3 years old.	865	950	Aug. 26, 1897	Killed October 27, 1897, lesions same as preceding.
Bovine III.	4	7	5th	9	2 c.c.	No 71	Bull, yearling.	645	575[1]	Aug. 26, 1897	Died September 12, 1897, disseminated tuberculosis of lungs and liver.
" IV.	4	3	5th	9	2 c.c.	No. 88	Cow, about 12 years old.	850	850	Aug. 26, 1897	Killed October 27, 1897, many minute tubercles in lungs, tuberculous deposits on pleura.
" V.	4	3	5th	9	2 c.c.	No. 63	Cow, about 6 years old.	875	870	Aug. 26, 1897	Killed October 27, 1897, disseminated tuberculosis of lungs and spleen.

[1] Two days before death.

There is proof, furthermore, of the existence of slightly varying characters, even within the varieties proposed. Among the bovine forms studied slight variations in virulence were noticeable. Among the sputum forms variations in size, in capacity for cultivation, and in pathogenic activity have been observed. The differences between Sputum Culture I., on the one hand, and Sputum Cultures II. to VII., on the other, are quite pronounced. In spite of these variations mammalian tubercle bacilli may still be considered as forming a fairly compact group when compared with the tubercle bacilli of birds, which are but slightly virulent toward the guinea-pig, so susceptible to the mammalian type.[1]

In regard to the bovine and the sputum varieties, I have in a former paper pointed out certain differences of behavior in the body which may be of considerable significance in explaining their divergent characters. In an organism like the human body, manifesting a certain amount of resistance to the tubercle bacillus, the sputum type multiplies only to a limited extent, unless it can produce dead tissue or gain an exit upon mucous membranes secreting pathological products, where it seems to flourish as a saprophyte. Similar conditions are now and then observed in animals inoculated with human bacilli. Immense numbers of bacilli are occasionally found in necrotic foci, but very few in the surrounding zone of living tissue. In the many sections examined recently the necrotic foci were the ones in which human bacilli were to be found, if detected at all. The bovine type differs from the former in a far less saprophytic growth. In the pathological secretions and in the caseous masses the bacilli are relatively scarce. This difference may be a result of their adaptation to the bovine body in which cavities in the lungs and catarrh of the air-tubes are far less common. In other words, certain differences in the type of reaction tend in the one case to make the human bacillus more saprophytic, the bovine more parasitic.

Coming to the more practical aspect of this subject we may present, in view of the relationship between the bovine and the sputum variety of the tubercle bacillus, two propositions for discussion:

[1] I have, unfortunately, been unable to study avian bacilli in connection with the series of this article, because opportunities for making cultures from fowls were wanting. The study of cultures of unknown or indefinite history I have not regarded as likely to yield trustworthy evidence.

1. The sputum bacillus is incapable of finding a foothold in the bovine body.

2. The bovine bacillus may pass to the human subject, owing to its higher pathogenic power.

The transmission of human tuberculosis to cattle has been experimentally essayed by Bollinger, Crookshank, Baumgarten, Sidney Martin, the writer, and Frothingham.

Bollinger[1] reported in 1894 an experiment performed in 1879. A calf, three months old, was inoculated into the peritoneal cavity with fluid from a tuberculous human lung. The calf was killed in seven months. On the mesentery and the peritoneal covering of the spleen there were found pediculated tumors from the size of a pea to that of a walnut. The microscopic appearance corresponded completely with that of the spontaneous pearly disease of cattle. The retroperitoneal and mesenteric glands were tuberculous. All others were normal. The little drawing which Bollinger published with the article gives one the impression of smooth roundish tumors similar to those I have described as resulting from the injection of Sputum Cultures IV. and VI. They have not the nodulated appearance presented by the spontaneous eruptions or those produced by bovine cultures.

Crookshank[2] injected sputum containing numerous tubercle bacilli into the peritoneal cavity of a calf. The calf died after a prolonged illness on the forty-second day.

"Extensive lesions were discovered at the post-mortem examination. The mesentery was adherent to the rumen; the liver was adherent to the diaphragm. There was extensive tubercular deposit at the seat of inoculation and an abscess the size of a walnut. Extending over the mesentery from this point there were hundreds of wart-like, fleshy new growths, some quite irregular in form, others spherical or button-shaped. There were similar deposits on the under surface of the liver, on the spleen, in the gastro-splenic omentum, and on the peritoneal surface of the diaphragm. The spleen was adherent to the rumen, and on dissecting away the adhesions another abscess was opened. On the under surface of the liver was a third abscess about the size of one's fist, which burrowed in the depth of the liver-substance.

"On microscopic examination extremely minute tubercles were found disseminated throughout the lungs and liver; tubercle bacilli were found in these organs and in the peritoneal deposits. The pus from the liver-abscess contained streptococci. The calf died of pyæmia, a result to be anticipated if sputum be employed for inoculation; but sufficient time had elapsed for pronounced local infection, leading to acute miliary tuberculosis."

I quote this experiment more fully so that it may discredit itself as a means of deciding whether sputum can produce general miliary tuberculosis

[1] Münchener med. Wochenschr., 1894, No. 5.

[2] Transactions Pathological Society, London, 1891, 332.

in cattle. We know, as yet, too little of the influence of concurrent infections to place any reliance upon the outcome of this experiment as a demonstration of the transmissibility of human bacilli to cattle.

Baumgarten[1] briefly mentions an experiment in which human bacilli in cultures had but little local effect after intraocular inoculations upon a calf. Material from a bovine pearly nodule produced typical local and general miliary tuberculosis in another calf.

Sidney Martin[2] fed one kilogramme of tuberculous material from a cow to four calves at one meal with their food. Within four weeks tubercles were found in Peyer's patches, mesenteric and bronchial glands, and in the lungs of one animal. After eight weeks another calf presented the same lesions plus tuberculosis of the posterior mediastinal and the cervical glands. The third calf, killed after twelve weeks, showed ulceration of the small intestine and cæcum and lesions of the pleura, besides those mentioned above. The fourth calf, killed after thirty-seven weeks, had tuberculosis of the pleura, in addition to that of the various lymph-glands already mentioned.

Four calves were fed at one meal with 70 c.c. of sputum containing a large number of tubercle bacilli. Three calves, killed after four, eight, and twelve weeks respectively, had fifty-three, sixty-three, and thirteen nodules respectively in the small intestines, chiefly in Peyer's patches. In the fourth calf, killed after thirty-three weeks, no lesions were found.

Two calves received at one feeding 440 c.c. of sputum containing a large number of tubercle bacilli. In one calf, killed in eight weeks, thirteen tuberculous nodules were found in the intestine. The mesenteric glands were also affected. The other calf, killed in nineteen weeks, was found without any lesions.

The author infers from these experiments "that in the case of tuberculous sputum we are dealing with material which is less infective to calves than bovine tuberculous material."

Frothingham[3] carried out some experiments of a similar character for the Massachusetts Cattle Commission. A culture of human bacilli was used, isolated from the liver of a child and about one year old. Two calves, three months and three weeks old respectively, received suspensions of the culture into the peritoneal cavity. In both only slight local nodules were produced, some resembling spontaneous tubercles, others tending toward granulation-tissue. Two calves, three weeks and two months old respectively, were inoculated into the trachea. In one case the large local abscess in the muscles of the neck indicated a deposit there of much of the material destined for the lungs. In the liver and lungs a small number of minute tubercles, devoid of tubercle bacilli, were found. In the other calf lesions were absent. Thus, in spite of the immature age of these animals, the tubercle bacillus

[1] Jahresbericht for 1891, footnote, p. 666.

[2] Report of the Royal Commission on Tuberculosis, 1895. Appendix, 18.

[3] Report of Massachusetts Cattle Commission for 1897. See also Zeitschr. f. Thiermed., 1897, 330.

may be said to have had but a trifling local effect on them. The tests on guinea-pigs indicate a very attenuated culture. Three additional calves inoculated subcutaneously with sputum containing many tubercle bacilli showed lesions equally slight.

The defect of most of these tests is the absence of parallel experiments with bovine tubercle bacilli. Inasmuch as we do not yet know anything concerning the relative resistance of cattle to tuberculosis at different periods of life, nor the relative effect of cultivation on the bacilli and of different modes of inoculation, such parallel experiments are quite essential. Of these few experiments, Bollinger's is the only one which might be regarded as favoring the susceptibility of very young cattle to human bacilli. Even here the disease penetrated only to the mesenteric and retro-peritoneal lymph-glands.

A summary of the inoculation experiments made by the writer upon cattle has already been given. Here we need simply to report the most salient features. These are:

1. The purely local, restricted character of the lesions in cattle due to sputum bacilli. Lesions were not found beyond the place of deposit or in the lymphatic glands to which these are tributary, excepting in one animal (Sputum V. Culture). In this case we find a multiple tubercular focus measuring *in toto* about 1 to 1.5 c.m. in one of the dorsal mediastinal glands. This is the only affected gland found in the five cases. Considering the fact that the bacillus was one of the more attenuated, that, on the other hand, the animal was fully four years old, I am strongly inclined to look upon this isolated instance of lymph-gland infection as a latent infection with bovine bacilli which was probably favored by the depressing effect of the injection into a slight activity. I take this ground because of its isolated occurrence and the very typical bovine character of the lesions. It is not unusual for such a slight lesion to be encountered in animals which have failed to react toward tuberculin, for experimenters agree upon a margin of error of 5 to 10 per cent., the lesions found in such cases being usually quite insignificant. Had the culture used not shown a virulence not only not above but slightly below the average virulence of the other sputum bacilli, as tested on a rabbit and on guinea-pigs, the above inference could not be justly drawn.

2. The atypical tissue changes induced by the sputum bacilli which tended chiefly toward granulation-tissue. Tubercle formation recog-

nizable as such was uncommon. Besides the lymphatic focus cited above as of doubtful origin, tubercles approaching nearest the bovine type were encountered in the primary lung focus in the youngest animal (Sputum IV.).

Some writers, including Bollinger and Baumgarten, are inclined to regard the pediculated masses produced on serous membranes by the inoculation of sputum or of cultures (Sputum IV., VI.) as something specific and as deciding positively the transmissibility of human bacilli to cattle. Leaving aside the abortive, atypical, microscopic structure of the pediculated masses produced in the writer's series, and assuming that the inoculation of young calves may furnish lesions of a more typical character, we may present anatomical and histological facts which go far to show that there is nothing characteristic or peculiar about them or about pearly disease in general.

On the omentum and the pleura of cattle not tuberculous there may exist in many cases patches of delicate filamentous fringes, probably in all cases the result of some local inflammation. These fringes are microscopic in size and only visible to the naked eye when they are present in large numbers and congested. My attention was first called to them in the study of Texas fever. Owing to the congestion of the whole portal system, these fringes, massed together, appeared as red patches on the omentum. The microscope showed them to consist of a capillary encased in a sheath of delicate fibrillar tissue, and the latter covered by the endothelium of the peritoneum. Recently I have demonstrated the same fringes in slightly raised, reddened patches of the costal pleura in otherwise healthy cattle. Here they are quite inconspicuous, but may be demonstrated by seizing the surface of the membrane with delicate forceps. Invisible threads hold the latter near the membrane. In the fresh condition their structure is like that of the fringes on the omentum. In some I was unable to demonstrate a capillary. In all cases they consist of the wavy fibrillar tissue devoid of nuclei, but containing at times a few granule cells, recognized as acidophile leucocytes in stained sections. In sections, these fringes could be traced from their attachment to the serosa. The fibrillar tissue is directly continuous with the subserous layer of like tissue, and the endothelial layer of the pleura is continuous over these fringes. The immediate union of fringes containing a capillary with the pleura was not demonstrated in the limited number of sections examined. Besides those of the simplest structure, others are seen in an active state of proliferation and infiltrated with lymphoid and acidophile leucocytes.

These fringes or filaments, probably the result of traumatic and other inflammation, form an excellent place of attachment for the injected tubercle bacilli. Here processes of epithelioid and giant-cell formation go on rapidly when bovine bacilli are present, whereas the sputum bacilli tend to lead only

to granulation-tissue with slight abortive tubercle formation. These new formations, subject to pressure and friction, may undergo hemorrhage, anæmic necrosis due to twisting of the pedicle, and subsequent increase of the connective-tissue stroma around the dead fringe. In this way those peculiar, smooth nodes probably arise which are briefly described under the cases inoculated with Sputum Cultures IV. and VI. It is furthermore evident, from the inoculation experiments, that, among other causes, the tubercle bacillus itself is one inducing the formation of granulation-tissue. The highly vascular, velvety layers of granulation-tissue carpeting the costal pleura in most of the cattle inoculated is a sufficient proof of the existence of this tendency. The pearly disease may thus be a product of at least two factors, the presence of this tissue as a result of former proliferation, and the inherent tendency of the serous membrane of cattle to respond by the formation of these vascular fringes to tubercles situated under the pleura and to bacilli discharged subsequently from such tubercles. But still other factors may be concerned.

That a certain retarded movement of the disease process may produce pearly disease in other animals has been answered in the affirmative for rabbits by Troje and Tangl.[1] These authors inoculated subcutaneously bacilli from cultures and material from the tuberculous lungs of rabbits which had been intimately mixed with iodoform and kept in the dark in contact with it for one or two weeks. In two rabbits, from two separate experiments, chloroformed respectively seven and nine months after inoculation, pediculated tubercles of the serous membranes were found. Those not containing angular concrements, and therefore sectionable, were peculiar in the possession of a very large number of very large giant cells.

These observations I am able to confirm by one case, the rabbit inoculated with the culture of Sputum VI. This rabbit was chloroformed three and one-half months after the intravenous injection of tubercle bacilli. Its weight had risen from 1305 to 2061 grammes. The notes on this case are, briefly, as follows:

Organs apparently unaffected (brain and cord not examined), excepting the liver, kidneys, and lungs. The liver contains a small number of 1 to 2 mm. centrally caseous foci. The kidneys show a considerable number of grayish, opaque, 1 mm. tubercles. The lungs collapse well. They are everywhere beset with translucent bodies, seen with some difficulty, owing to their glassy appearance. Some have a minute, pointlike, opaque centre. In the small cephalic lobes there are larger confluent patches, especially on the margins, of a peculiar grayish-translucent appearance. Sections of hardened tissue show the distinctly epithelioid character of the tubercular changes with very few giant cells. Necrosis only in the largest foci. Tubercle bacilli fairly abundant in the necrosed centres, elsewhere scarce. From the marginal tubercles fingerlike prolongations, precisely like those of the bovine pleura, project into the pleural cavity. They consist mainly of rapidly-proliferating connective-tissue cells embedded in a very delicately-fibrillar meshwork. The

[1] Deutsche med. Wochenschrift, 1892, 191.

basal portion of the fringe is partly covered with endothelium continuous with that of the pleura, and contains a number of capillaries in transverse section. Similar vascular fringes appear on the opposite margin of the same section.

It is not improbable that if this animal had been allowed to live as long as those of Troje and Tangl, tubercle bacilli would have found their way into these fringes and produced the so-called pearly disease. This rabbit was allowed to live longer than any other of the sputum series. We may thus assume that neoplasms of the pleura in rabbits may be looked for after the third month. These observations go far to show that the eruption of tubercles on the pleura is not so much an expression of peculiarity on the part of the tubercle bacillus as it is an expression of a certain grade of virulence of the bacillus in an organism possessing a certain grade of resistance to it. To these conditions may possibly be added a pronounced tendency in certain animals toward production of granulation tissue of a certain type on serous membranes.

Troje[1] has also described a rare case of pearly disease in man, affecting the pleura. Here, possibly, the previous existence of outgrowths, like the fringes on the serous membranes of cattle, may have been responsible for the peculiar localization of the tubercle bacillus.

Putting all the facts obtained by experiments on cattle together, it would seem as though the sputum bacillus cannot gain lodgement in cattle through the ordinary channels. These avenues, well provided with protective mechanisms, receive the bacilli probably one at at a time. However closely the sputum and the bovine bacillus may be related, it seems as if, under ordinary circumstances, the former would fall an easy prey to destruction. This inference will gain in weight if we bear in mind that the far more potent bovine bacillus produces in at least 50 per cent. of the spontaneously infected cattle a purely local disease, which probably would remain so if the animal were surrounded with favorable conditions.

The second and most important proposition, the transmission of bovine bacilli to the human subject, has been much discussed in recent years, without, however, bringing us any nearer to definite knowledge.

A recent compilation of cases of presumable transmission from cattle to man, both through wounds of the skin and through the digestive tract in milk, by Ravenel,[2] gives, perhaps, the most condensed account up to date. To these may be added a most interesting case reported by Coppez.[3] A girl,

[1] Loc. cit. [2] Journal of Compar. Medicine and Vet. Archives, December, 1897.

[3] "Un cas de tuberculose cutanée et oculaire sans manifestations viscérales." Rev. gén. d'ophthalm., xv. (1896), 433.

seventeen years old, had a wound on the palmar aspect of the third finger, between the second and third phalanx, which became infected with tubercle bacilli during milking. The original lesions gave rise, within six months, to over thirty-five subcutaneous abscesses, situated in different parts of the body. There were two on the right hand, four on the elbow, two on the shoulder-blade, several on the right cheek, two on the left palm, one on the back of the neck, a dozen on the buttocks and thighs, four on the left leg, three on the sole of one foot, and one on the big toe. Most of these were curetted and iodoform applied six months after the beginning of the disease. Subsequently more appeared, in all from sixty to sixty-six. The author describes the appearance of these foci as follows:

At a certain point, always in the neighborhood of a pre-existing focus, a thickening of the subcutaneous tissue appeared, associated with increased heat of the skin and pain on pressure. The heat soon disappeared, and a fluctuating livid tumor opened itself and discharged pus, and later a yellowish serum. These various abscesses healed slowly, and within a year all had disappeared. At no time could any visceral lesions be recognized, but one eye became involved. The nature of the affection was demonstrated by inserting some pus from an abscess into the eye of a rabbit. There was but slight reaction at first. Subsequently the whole eye became diseased, the lymph nodes of the neck greatly enlarged. After several months death ensued.[1]

If bovine bacilli may invade the human body without let or hinderance, we have not only food infection through milk and milk products to guard against, but also the inhalation disease, to which men are exposed in stables containing tuberculous cattle. What proportion of tuberculous subjects may derive their infection from these sources we do not know. Now that we have established some fairly pronounced differences between bovine and sputum bacilli, the whole discussion might be cut short by the suggestion that the time has come to stop citing old and doubtful cases, and to go to work to study with care the tubercle bacilli from cases of supposed animal origin, so

[1] In an article written just before the discovery of the tubercle bacillus, Creighton ("Bovine Tuberculosis in Man," Journ. Anat. and Physiology, xv. (1880), 1–177) describes twelve cases, following one another quite closely in the same hospital, which he considers to be afflicted with the bovine disease. This type of tuberculosis was characterized by eruptions on the serous membranes, large, grayish-white medullary tumors in the lungs, frequently assuming the form of a wedge, and by certain microscopic peculiarities. These cases may have been due to some other organism. Quite recently Askanazy ("Ueber tumorartiges Auftreten der Tuberkulose," Zeitschr. f. klin. Med., 1897, xxxii. 360), besides giving a good bibliography, cites two cases in full, in which the peculiar type of disease leads him to suggest their relation to pearly disease in cattle. These articles simply impress upon the reader that the true interpretation of such cases will remain obscure until the etiological agent has been studied. The variable character of the tissue reaction to the tubercle bacillus, according to the species, deprives the pathological study, taken alone, of any decisive value.

that some experimental trustworthy basis may be formed upon which to found statistics. While this is, in truth, what will have to be done, and is the goal which has been aimed at from the outset in this tedious work, it will take much time and persistent attention to collect evidence of this kind. In the mean time the relation of bovine to human tuberculosis must be somehow defined before a fairly helpless and frightened public. It seems to me that, accepting the clinical evidence on hand, bovine tuberculosis may be transmitted to children when the body is overpowered by large numbers of bacilli, as in udder tuberculosis, or when certain unknown favorable conditions exist.[1] To prevent this from occurring, a rigid periodic dairy inspection, and the removal of all suspicious udder affections and all emaciated animals, is as much as public health authorities can at present demand. Any measures beyond these belong to agriculture, with which the public health has no business to meddle without endangering the chances of gaining authority to enforce its own necessary measures. If the evidence gained by pathology in the future should reveal a greater danger than is here assumed, the scientific basis of such evidence will, I think, force all additional measures needed.

But for the student of etiology the problem does not end in the differentiation of varieties. It reaches out much farther than this, and involves some puzzling questions. The most important one bears on the possible changes which the tubercle bacillus may undergo during its prolonged sojourn in the human body. I have already referred to one phase of this question in mentioning the saprophytic growth of the sputum bacillus in the affected lungs and necrotic tissue as contrasted with its slight multiplication in living tissue and with the generally slight multiplication of the bovine bacillus in the tissue of cattle. This question is a very complicated one, and nothing is easier than to reason in a circle about it, because of the entire absence of data. The first hypothesis to be considered is that which assumes the conversion of the bovine bacillus into the sputum bacillus in the human body. This hypothesis would deny us all possibility of utilizing different characters of tubercle bacilli in tracing their source. If the bovine variety may enter the digestive tract as such, and after a more or less prolonged interval emerge from the secondarily affected lungs

[1] Probably much the same as in glanders. The number of glandered horses in certain places is out of all proportion to the cases of men who are continually handling and cleaning them.

as the sputum variety, we may as well give up all further study of the tubercle bacillus. The accumulated evidence of bacteriology is opposed to this view. Nevertheless it has been unwittingly assumed by Klebs in considering intestinal infection with the bovine bacillus as a common cause of tuberculosis.[1] As a support of the view that tubercle bacilli change but very slowly, I may again mention the inoculation test upon a rabbit of Bovine Culture I. About three years after the first test the second test resulted in only a very slight prolongation of the disease. The first rabbit succumbed in seventeen, the second in twenty-two days. It was thus after three years of artificial growth still far above sputum bacilli in pathogenic power.

The question of phthisis as secondary to infection by way of the digestive organs is, however, one needing more attention, for experimental results in this direction are quite suggestive. In all mammals the lungs are evidently the most favored place of tubercle bacilli, and wherever the latter may be deposited, they sooner or later, unless the disease is checked, reach that organ where the process spreads more rapidly than elsewhere. This march from the place of infection is not infrequently partially concealed by reparative processes. A recent case in point is that of a guinea-pig inoculated with a culture of Sputum VI.:

Aug. 26, 1897. Male guinea-pig, weighs 420 grammes. Receives subcutaneously in the flank 0.5 c.c. of a clouded suspension of tubercle bacilli (Sputum VI.) nine days old.

Nov. 8. Breathing now labored; had been active since inoculation.

11*th*. Respiration labored and almost convulsive, hence chloroformed; weight, 431 grammes.

No ulcer at point of inoculation.

Kneefold glands of this side as large as peas, yellowish in color, consisting of a thin-walled sac and homogeneous contents, resembling thick cream. Kneefold glands of opposite side moderately enlarged, but without necrotic changes. The pelvic, renal, retrogastric, and mesenteric glands enlarged slightly, but without necrosis. Spleen small; shows grayish specks disseminated through it. Liver and kidneys appear normal; two small tubercles on left testicle. Lungs do not collapse; they feel firm everywhere. On section, most of the lung-tissue is consolidated, of a grayish-white color. No fluid expressible from air-tubes. In sections of the lungs the infiltration consists chiefly of epithelioid cells, with smaller, more deeply stained nuclei intermingled or in patches. No necrosis. The liver was, through an oversight,

[1] Die kausale Behandlung der Tuberkulose, 1894, 34.

not preserved. The spleen shows in each follicle a rarefied area occupied by epithelioid cells and a few tubercle bacilli. No necrosis.

In this susceptible animal the only lesions threatening life or even conspicuous were those in the lungs. Those in the spleen were slight, possibly stationary. The disintegrated superficial glands might have discharged outwardly later on and healed. This is but one of a number of cases I have observed in the past ten years in which there was progression in the lungs with almost complete destruction of the organ and retrogression elsewhere, showing itself in the liver by the shrinking and furrowing of the organ.[1]

With the two facts before us that tubercle bacilli gravitate as it were toward the lungs in all the susceptible mammals, and that they may conceal their movements in the body quite effectually, we must regard infection through the digestive tract as a source of phthisis at least deserving more attention. The only question to interest us here is the relation of the bovine bacillus to this process. Only much painstaking work will enable us to learn whether the human body can produce such a good modification of the bovine bacillus or not.

Another more acceptable hypothesis concerning changes in the tubercle bacillus would assume a slow, continuous modification, which in the past has developed the sputum variety on the one hand and the bovine variety on the other. The future may enable us to establish not only other varieties linked to certain animal species, but also varieties which produce slightly different forms of disease in man himself.[2] The saprophytic life of the sputum bacillus in phthisis may be the cause of a very slow downward descent of its invasive power, which in the course of one or more generations may become perceptible both to the bacteriologist and to the clinician, and express itself to the statistician in the gradually falling curve of tuberculosis, as shown by the vital statistics of the past forty years.[3]

The outcome of such slow changes would lead to the establishment

[1] This generalization has been recently emphasized by Spengler (Zeitschr. f. Hygiene, 1897, xxvi. 321) as follows: The retarded course of an inoculation-tuberculosis expresses itself without exception in a (greater) prominence of the lung disease with simultaneous retardation of the liver and spleen affection.

[2] More recently I have studied cultures of tubercle bacilli from a rapidly progressive tuberculous gland of the neck in an adult. These bacilli are slightly *less* virulent than the sputum bacilli described.

[3] S. W. Abbott. "The Vital Statistics of Massachusetts." Report of the State Board of Health for 1896, pp. 787–88.

of numerous minor varieties, because of the great opportunity which tubercle bacilli have in our congested, abnormal city life of selecting their variously predisposed victims. Thus the more attenuated varieties may find their invasion obstructed in the more vigorous, but not in children or certain predisposed individuals. It is needless for me to illustrate these possibilities still further. They have their parallels in nature all about us. Only one practical suggestion may be made in view of the probable discovery of minor varieties of human bacilli. Tuberculous patients should not be indiscriminately exposed to other tuberculous patients simply because both are affected with a disease which bears the same name.[1]

A more exhaustive experimental study of the tubercle bacillus away from the many variable factors acting upon the human body, which will lead to a better standardizing of virulence or invasive power, may help these speculations to find some substantial basis. That much is still to be learned concerning the etiology is evident from the want of unanimity as regards the channels of infection. The views of Koch and his followers of the transmission of the infection in dust and spray would tend to favor the hypothesis of gradual attenuation and of the production of minor varieties. Baumgarten's hypothesis of the transmission of the tubercle bacillus from parent to child before birth implies the transmission of tubercle bacilli either in a continual struggle with living tissue or else remaining in situations where the bacilli cannot multiply, and hence where a tendency to loss of invasive power by saprophytic growth is impossible. The occasional entrance of bovine bacilli into the human body might open the way for the introduction of a virus of a higher level, provided opportunity for subsequent transmission be afforded.

If in this brief summary I have presented nothing but problems to

[1] A beginning in this comparative study of different clinical types of tuberculosis has been made by Auclair (Arch. de méd. exp., 1897, ix. p. 1124). This article, which came to my notice after the completion of this manuscript, describes four cultures: one from a rapidly progressive tuberculosis of a gland of the neck, one from a slow phthisis, one from an acute meningitis, and one from true scrofula. On guinea-pigs the intra-abdominal inoculation of these cultures had nearly the same effect. Hence the author did not hesitate to regard them as identical in pathogenic power, in opposition to the views of Arloing, who considers the bacillus of phthisis and those of the surgical forms of tuberculosis of different virulence. Auclair did not inoculate rabbits, in spite of the fact that Arloing regarded them as the best means of differentiating the bacilli of the different forms of tuberculosis. My own results show that if the intra-abdominal inoculation of guinea-pigs is the only test made, practically no differences worth considering would appear between bovine and sputum bacilli as regards pathogenic power.

be solved and doubts to be entertained, I feel quite confident that the comparative study of tubercle bacilli will lead to some definite understanding on certain important questions, and eventually to more light on the whole subject of tuberculosis from the preventive as well as the therapeutic side.

The main questions proposing themselves to the investigator are:

1. The study of tubercle bacilli from different types of tuberculosis, to determine their relation to the sputum bacillus and the bovine bacillus as regards virulence.

2. The study of the bacilli in primary intestinal disease and in all tubercular disease in children in which the source of infection is assumed to be outside of the family and possibly in the milk.

In attacking these problems the investigator should either keep strictly to the methods suggested in this article if he wishes to use its results as a basis, or else, in all cases in which the bovine bacillus or one of abnormal virulence is suspected, he should study fresh cultures of the sputum bacillus side by side with the other.

A CASE OF MYCETOMA (MADURA FOOT).

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Mycetoma is a chronic inflammatory process, most commonly affecting the tissues of the foot, in which suppurative nodular swellings, sinus formation, and enlargement and distortion of the parts are prominent features. The bones may become involved and undergo a rarefying osteitis.

The affection is characterized by the presence in the diseased tissue and in the discharge from sinuses of peculiar granules, usually not more than one millimetre in diameter, but sometimes larger. These granules in certain cases are of a black color, of irregular shape, and are hard and rather brittle. In general, they resemble grains of gunpowder. In other cases the granules are whitish, grayish, or yellowish in color, and are of a soft or cheesy consistency. They have been compared to fish-roe in appearance. A very few cases are also recorded in which the granules were of a red color. There is no good evidence to show that more than one kind of granules are ever present in any one case of the disease.

On account of the fact that at least two very different kinds of granules are found associated with the lesions, two varieties or forms of the disease are recognized—the "melanoid" or black variety, in which the granules are black, and the "ochroid" or pale variety, in which the granules are white to yellow in color. A. Vandyke Carter, who was the first to show that mycetoma was a special pathological process and to name the disease itself and its varieties, considered the granules to be the cause of the affection, and regarded them as representing stages in the life-history of one and the same fungus. Carter claimed that he had cultivated this fungus, and that it grew as a pink

mould. This pink mould was studied by H. J. Berkeley, and named by him "Chionyphe Carteri." The connection between this pink mould and the granules was not clearly demonstrated, owing to the conditions under which the cultivation experiments were made, so that the pink mould has not been generally believed to represent the infecting organism in the process. There can be little doubt, however, that Carter saw and recognized in the black granules the same fungus elements which have been described by later observers. This is quite apparent from an examination of the plates in his monograph,[1] published in 1874.

It is now reasonably certain, however, that the organism of the black granules is of an entirely different character from the organism or organisms making up the pale or yellowish granules. Therefore, in summarizing the results of various observers who have studied the nature of these granules, observations on the black granules will be considered separately from those upon the pale or yellow granules.

The disease is endemic in India, and has been observed in Africa, Italy, and other tropical or subtropical countries. In America it is of very rare occurrence, only three undoubted cases in all having been reported up to the present time. These are the cases of Adami and Kirkpatrick,[2] of Hyde, Senn, and Bishop,[3] and of Pope and Lamb.[4] These were all of the ochroid variety of the disease. In a case reported by Kemper and Jameson[5] the diagnosis is open to serious question, so that it is not included in the list.

OBSERVATIONS ON THE GRANULES. *The Melanoid Variety.* Bristowe[6] studied the black granules in a single case. He found them to consist "of densely aggregated ramifying tubules" embedded in a dark-colored matrix. They frequently showed dilatation into round or ovoid cells. These structures he considered to be elements of a fungus identical with that described by Carter. No cultivation experiments were made. Bristowe's description and drawings of the microscopical appearance of the granules are very satisfactory. It is quite evident that he had before him the same organism as that seen by Carter in the black granules.

[1] A. Vandyke Carter. On Mycetoma, or the Fungus Disease of India. London, 1874.

[2] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1895. Montreal Medical Journal, January, 1896.

[3] Journal of Cutaneous and Genito-Urinary Diseases, 1896, xvi. 1.

[4] New York Medical Journal, September 19, 1896.

[5] American Practitioner, Louisville, 1876, xiv. 129.

[6] Trans. Path. Soc., London, 1871.

Hogg[1] also examined a case of the melanoid variety, finding also fungoid structures in the granules, which, to judge from his description, were evidently the same as those described by Carter and by Bristowe.

In 1888 Bassini[2] described a case of the black variety which occurred in Italy. The granules were found to be made up of a mycelium of filaments embedded in a dark-brown matrix. These filaments were septate, four to six millimetres in diameter, and showed irregular swellings. They had a general radiate arrangement in the granule. Besides the granules, Bassini noted the presence of strings or cords, made up of the same fungus filaments, embedded in a brown matrix. No spore-bearing organs were found, and no cultivation experiments were made. The mycelium was regarded as representing "an imperfect vegetative form of a fungus which, in a state of perfect evolution, would be furnished with a true reproductive apparatus." Leucocytes and young bloodvessels were noted in the tissues about the granules.

Kanthack[3] studied three cases of the melanoid variety in microscopical sections. In all of these cases he found that the black granules seemed to consist, in some instances, of a structureless, olive-brown, glassy or finely-granular material, in which were embedded hollow filaments of varying calibre, having a well-marked radial arrangement. Kanthack regarded these appearances as representing degenerative changes, and sought to show that the granules were made up of an organism closely related to actinomyces, as he had found in the case of the pale granules. It is manifest from his description, however, that he saw the same fungus mycelium in the black granules which had been noted by previous observers.

The latest and most satisfactory paper on the structure and nature of the black granules is that of Boyce and Surveyor.[4] They studied seven cases of the melanoid form, and found in all of them that "the black particles represent a curious metamorphosis of a large, branching, septate fungus." This fungus was embedded in or surrounded by a brown pigment substance, which was readily removed by "Eau de Javelle." The hyphæ showed great variations in the size and shape of their segments. They were branched and often disposed in a radiate manner at the periphery. No organs of fructification were observed. The fungus was not cultivated.

The Ochroid Variety. Carter's view that the pale particles represented a stage in the evolution of the same fungus as that making up the black granules has already been mentioned.

In 1870 Moxon and Hogg[5] examined a case of this variety. They found that the granules showed in some instances a texture of fine fibrils, but they were unable to come to any conclusions as to their nature.

[1] Trans. Path. Soc., London, 1872.
[2] Archivio per le scienze mediche, 1888, xii. 309.
[3] Journal of Path. and Bact., 1893, i. 140.
[4] Trans. of the Royal Society of London, 1894. Proc. Royal Soc., London, 1893.
[5] Trans. Path. Soc., London, 1870.

Kanthack[1] examined histologically twelve specimens of the ochroid variety, and states that "the parasite of the ochroid variety agrees morphologically and structurally with the typical and perfect ray fungus, and there can be no reasonable doubt that both belong to the same botanical group."

Vincent[2] found that the granules in a case of the pale form of the disease were made up of a streptothrix, which grew upon potato with a marked red color. In a later paper, published with Gémy,[3] Vincent reports isolating in cultures the same streptothrix from a second case.

Hewlett[4] examined two cases of the ochroid variety, and states that the granules were very like colonies of actinomyces in structure. He considered that the process was actinomycosis.

Boyce and Surveyor[5] studied eighteen cases, and conclude that "the white particles consist largely of caseous material and of the remains of a lowly-organized fungus, presenting in very many instances some of the characteristics of the fungus of actinomycosis." This organism they regarded as entirely distinct from that found in the seven specimens of the melanoid variety which they had examined.

Boyce[6] also reports having cultivated a streptothrix from a case of the ochroid variety. This streptothrix differed in its cultural peculiarities from other similar organisms.

Adami and Kirkpatrick[7] conclude, from an examination of the case of the ochroid variety observed in Canada, that the granules "were identical in general appearance with actinomyces, forming lobate, reniform masses, with central dense mycelium and a radiate arrangement of filaments or clubs around the periphery. These clubs, however, were larger than those of actinomycosis."

Bishop,[8] in the paper published with Hyde and Senn, gives the results of his microscopical examination of a case occurring in Chicago. The granules by direct examination were made up of a dense granular central portion and a more transparent peripheral portion, in which an obscure radial striation could be observed. No clubs were observed at the periphery. In sections of the tissues the granules consisted of more or less rounded masses, often having a scalloped border and occurring singly and in groups. The central portions stained faintly with hæmatoxylin. Under a high magnifying power delicate filamentous threads, having more or less of a radial arrangement, were to be made out in the masses, and, at the margins of some, delicate radiating lines. There was much to suggest actinomycosis. The tissue changes consisted essentially in the formation of granulation tissue in which giant cells were present.

From a consideration of the results of this list of observers it is quite evident that the disease known as mycetoma is due to at least

[1] Loc. cit.
[2] Annales de l'Inst. Pasteur, 1894, xiii· 129.
[3] Annales de dermatologie et syphiligraphie, Paris, Nov. 1896, 3me sér., t. vii.
[4] Trans. Path. Soc., London, 1893.
[5] Loc. cit.
[6] Hygienische Rundschau, 1894, iv. 529.
[7] Loc. cit.
[8] Loc. cit.

two different organisms, or, in other words, that the black granules of the melanoid form are composed of an organism entirely different from the organism or organisms making up the pale or ochroid granules.

There can be little doubt that the melanoid granules are composed essentially of a fungus or a hyphomycete, and that probably one and the same fungus has been seen by all observers.

The chief thing lacking in these studies of the melanoid granules has been the growing of this fungus. This cultivation has been accomplished in the case reported below.

As to the nature of the granules in the ochroid form it is difficult to form an opinion in some of the cases. It seems clear that, in most of them at least, the granules are composed of organisms of the streptothrix group, to which actinomyces are now generally thought to belong, and not to the more highly organized hyphomycetes. That some of the cases of the ochroid variety are nothing more or less than actinomycosis seems not unlikely.

On account of the rarity of this disease in America, and because of the interest attaching to the parasite, the following case is reported:

CASE. *Clinical History.* The patient, an Italian woman, aged twenty-six, was admitted to the service of Dr. H. H. A. Beach, in the Massachusetts General Hospital, December 29, 1897. She was first seen in the out-patient department by Dr. C. A. Porter, who recognized the condition as probably Madura foot. The tissues of the left foot in the region of the base of the second and third toes on the plantar aspect presented a swollen appearance, with desquamation of the epithelium. In the skin over the swollen area there was a small sinus, from which exuded on pressure a dirty-grayish fluid, containing some black, hard, irregular granules, like grains of gunpowder. On the dorsum of the second toe, near its tarso-metatarsal joint, there was a small ulcer.

The disease was first noticed in July, 1897. The patient had lived in America five years. A piece of tissue was excised from the second toe for microscopical examination, and from the results of this, as well as from the appearance and character of the black granules associated with the condition, the diagnosis of mycetoma, or Madura foot, of the melanoid variety was made. Amputation of the four toes, together with a part of the four corresponding metatarsal bones, was performed by Dr. Beach.

The dissection of the amputated part showed the following conditions: In the soft tissue of the plantar side of the foot near the tarso-metatarsal articulations and immediately beneath the skin was a

pigeon's-egg-sized, ovoid tumor nodule, sharply defined from the surrounding tissue. (Plate I., Fig. 1.) This nodule on section consisted of a soft, in places gelatinous, myxomatous-like tissue, traversed by an indefinite reticulum which divided it into indefinite small areas; in these areas were embedded black, irregular granules less than a millimetre in diameter, resembling grains of gunpowder. These granules occurred singly and in groups. In one or two places the tissue of the nodule was opaque and yellowish, as from necrosis. Two other similar nodules of small size, containing black granules, were also present. One was situated in the soft tissue of the dorsum of the foot, near the base of the second and third toes; the other in the soft tissue of the first phalanx of the second toe. The larger of these nodules was about the size of a pea. The bones were not involved.

The Structure of the Black Granules. Macroscopically the granules are of an irregular or mulberry shape, of a black or dark-brown color, and usually less than one millimetre in diameter. They are sometimes bound together by shreds of tissue or of exudate. They are hard, rather brittle, and are not readily broken up under a cover-glass.

Microscopically they present the appearance of irregular, lobate masses of a dark-brown or black opaque substance. Upon being broken up and examined with high magnifying power, little more than indefinite, brown, somewhat refringent masses can be made out. Occasionally structures suggestive of fungus may be seen, but there is little else to indicate a vegetable nature. They are very resistant to most reagents, but by soaking them for a few minutes, with or without heating, in the ordinary hospital solution of sodium hypochlorite, they lose their brown or black color and become more or less completely white and soft, according to the duration of the action of the reagent. A strong solution of potassium hydroxide also softens them to a certain extent, but does not bleach them so quickly.

Granules from the hardened specimen, bleached and softened as above outlined, when crushed and dissociated under a cover-glass, are found to consist of a mass of fungus structures together with more or less brown pigmented embedding, or investing material, as described and figured by Boyce and Surveyor,[1] and others.

[1] Loc. cit.

Under a high magnifying power (Plate II., Fig. 7) the greater part of the mass of the granules is seen to consist of ovoid or rounded, translucent bodies of varying sizes, closely packed together, having homogeneous interiors or containing a few refractive granules. Among these bodies typical septate, branching hyphæ may be seen, sometimes showing dilatation or varicosities of their segments. The ovoid or rounded bodies seem to be dilated or degenerated hyphal segments, for not only may they be seen in continuity with the hyphæ, but transitions between them and the hyphæ with swollen segments may be made out.

The periphery of the granules has the appearance of being made up of closely set, radiating hyphæ, usually showing more or less swelling or degenerative changes in their segments.

No undoubted spore-bearing organs were observed, but occasionally a large spherical, thick-walled body containing smaller rounded or ovoid or elongated refringent bodies was observed. These were regarded as representing some peculiar mode of growth or an "involution," rather than spores and spore-bearing organs.

In specimens treated with caustic potash solution, when the removal of the interstitial pigmentary substance is not complete, branched hyphal tubes may be made out embedded in a brown refringent substance.

The test for hæmin in the black granules was negative.

In sections of the tissues, under the microscope, the granules are seen as rounded, lobate, reniform, or irregular bodies, of a more or less reticular structure in general (Plate I., Figs. 2 to 6; Plate II., Fig. 8). They are deeply stained by the basic aniline dyes, but are not stained by hæmatoxylin.

In sections stained with the latter they appear to be chiefly composed of a brown-colored, somewhat hyaline substance, arranged throughout the main portion of the granules in the form of a reticulum and in indefinite or rounded clumps. This substance at the margin may merge into a narrow zone of yellow, very hyaline refractive material, in which more or less of a radial striation may sometimes be apparent.

The results of the study of the granules in sections stained in various ways may be summarized as follows:

The granules, as a rule, are made up of a central portion and a

cortical portion or rind, without any definite separation between them. In the central portion are usually branching trabeculæ and rounded masses, composed of a hyaline substance, in the midst of which are numerous structures like fungus elements, cut in various planes. In some instances the central portion is made up mainly of an amorphous or indefinite material with only a few fungus hyphæ. In general the central portion is less dense in structure than the cortical portion or rind. The latter in most cases consists of a hyaline material, continuous with the hyaline trabeculæ of the central portion, in which fungus elements are embedded, sometimes arranged more or less in a radiate manner, sometimes not. The margin is irregularly scalloped or dentated. In some cases the cortical portion seems to be made up of more or less atypical hyphæ and elongated processes of hyaline substance radially disposed. In a very few instances the granules appear in the sections as irregularly shaped masses of homogeneous, hyaline or fine granular material, in which unstained or empty fungus tubules or hyphæ are embedded.

In brief, it may be said that the granules are composed of a mycelium of hyphæ or fungoid elements, more or less degenerated, embedded in or surrounded by a hyaline brown-colored refringent substance, which itself forms more or less of a reticulum.

The Gram stain and the Weigert fibrin stain, or modifications of them, stain the substance of the granules to a variable extent depending on the amount of the decolorizing agents applied. The marginal portions of the granules hold the stains longest. In only a very few instances could the hyphæ be differentially stained by these methods.

Cultures. About sixty-five of the black granules were planted in various culture-media, after having been washed in sterilized bouillon to remove contaminating organisms as much as possible. Nearly all of these granules were taken from freshly cut portions of the nodules of the foot after amputation. From approximately twenty-five of the sixty-five granules a growth of a hyphomycete was obtained. The original cultures, with one or two exceptions, showed more or less contamination with the staphylococcus albus, which was abundantly present in the diseased tissue. The exceptions were in the cases of one or two grains, obtained from the sinuses before the amputation and after peroxide of hydrogen had been used at intervals in the sinuses. This reagent had probably destroyed most or all of the pus

cocci adherent to the grains, so that the washing in sterile bouillon sufficed to render it free from living contaminations.

The growth in all cases began from the grain and appeared after about four or five days or later. On solid culture-media it first appeared as a tuft of delicate whitish filaments springing from the black grain. These in the course of a few days increased in number and length, and in the case of the potato formed a dense whitish or pale-brown felt-work or membrane, having a tendency to spread widely (Plate II., Fig. 12).

Granules planted in potato infusion, in which the contaminating cocci grew only feebly, and granules obtained free from contamination and planted in bouillon, showed, after four or more days, a faint grayish halo about their peripheries. In the course of some days this increased in size and was seen to consist of long delicate radiating filaments (Plate II., Fig. 9), which grew in length until they reached the wall of the tube and produced the appearance of a powder puff-ball, with the granule in the centre (Plate II., Fig. 11). Granules were readily obtained free from bacterial contamination and planted in bouillon for development by selecting those grains which, after remaining on solid culture-media for several days, were well separated from colonies of cocci. Many of the granules—*i. e.*, about forty out of the sixty-five—failed to develop any fungus. This fact bears out the idea that many of the fungus elements in the granules are degenerated, as has been mentioned.

The characters of the hyphomycete may be summed up as follows:

Morphology (Plate II., Figs. 9 and 10). Long-branching hyphæ from 3 to 8 μ in diameter. In the younger ones delicate transverse septa are present. In the older forms there may be swellings at these points and the hyphæ may appear as a string of oval-ended, plump segments. The filaments have a definite wall, and in their interior granules or pale areas may be seen. The branching occurs by the formation of lateral outgrowths or buds. No spore-bearing organs were observed.

Potato. It forms a dense, widely spreading, coherent membrane, or layer, of velvety surface, pale brown in color throughout its central portions, and white at its peripheral portions. A marked feature is the appearance of small spherical globules or droplets of dark, coffee-

colored fluid on the surface of this layer. The potato takes on a dark-brown color and becomes very moist (Plate II., Fig. 12).

Bouillon. The growth always proceeds from the planted material, whether grain or fragment of mycelium, in the form of fine radiating filaments, and soon produces a puff-ball appearance (Plate II., Figs. 9 and 11). Eventually the whole area of fluid is filled up with the radiating mycelium and a definite mycelial layer is formed at the surface. The medium acquires a deep coffee-brown color.

Potato Infusion. This was prepared by boiling about 20 grammes of potato in water, filtering and making up to 1000 c.c. without neutralizing, as used by Vincent.[1] In this the growth proceeds as in bouillon except that no surface layer is formed. A peculiarity, however, noted in old cultures, consists in the appearance of numerous black granules about one millimetre or less in diameter, in the midst of the mycelium.

These granules consist of closely packed spherical or polyphedral cells, together with some short, thick, segmented hyphæ. The walls of these cells have a black appearance and masses of them are black and opaque under the microscope. They seem to represent masses of interlacing hyphæ whose segments have been much shortened and widened, and otherwise changed.

These black masses were kindly examined by Prof. W. G. Farlow, of Harvard University, who considered them to be "sclerotia."

Agar-agar (plain and glucose). The growth appears as a meshwork of widely spreading filaments, of a grayish color, on the surface of the medium. In old cultures black "sclerotia" are found, as in the potato infusion. In stab-cultures growth appears only at the surface.

No results were obtained from the inoculation of animals with the original granules or with cultures.

Pathological Histology. The tissue composing the nodules consists essentially of a formation of more or less atypical connective tissue, in various stages of development, in which foci of suppuration are present in association with the granules.

Some of the granules lie in small cavities, containing polynuclear leucocytes, loose epithelioid cells, and cellular detritus. These cavi-

[1] Loc. cit.

ties may be lined either by a wall of vascular granulation tissue or by masses of epithelioid cells, together with multinucleated giant cells (Plate I., Figs. 2 to 4). Other granules are closely invested by a zone of epithelioid and giant cells, and outside of this there may be an infiltration with lymphoid and plasma cells. The nodule thus formed about the granule resembles very closely a tubercle in structure. This tubercle-like formation is shown in Plate I., Figs. 5 and 6. The giant cells are often of large size and may have a peripheral arrangement of their nuclei. They are a very prominent element in the lesions.

The primary effect produced by the parasites upon the tissues seems to be the development of nodules of epithelioid cells and of giant cells from the tissues immediately about them. Later, suppurative processes occur in the nodules, and abscesses are formed, which in time give rise to the development of granulation and connective tissue in large amount.

The writer is under obligations to Dr. H. H. A. Beach, of the staff of the Massachusetts General Hospital, and to Prof. W. G. Farlow, of Harvard University, for courtesies shown him in connection with the study of this case.

The photographs which accompany this paper were made by Mr. Louis F. Brown. For valuable instruction and suggestions in their preparation the writer is greatly indebted to Mr. John G. Hubbard, of Brookline, Mass.

DESCRIPTION OF PLATES.[1]

PLATE I.

FIG. 1.—Portion of amputated part showing the black granules and general character of the lesions as seen with naked eye.

FIG. 2.—Section showing black granules and general features of the lesions as they appear under a low magnifying power—Zeiss a_2.

FIGS. 3, 4, 5, and 6.—Sections showing the granules and surrounding cells. All with the exception of Fig. 4 taken with Zeiss apochromat. 16 mm. Fig. 4 taken with Zeiss apochromat. 4 mm. Figs. 5 and 6 represent the tubercle-like nodules, with the parasite in the centre, as described in the text.

PLATE II.

FIG. 7.—Fungus elements from a granule after bleaching and softening with sodium hypochlorite solution. A branching, septate hypha is shown. Zeiss apochromat. 4 mm.

FIG. 8.—Section showing margin of two continuous granules, highly magnified. Zeiss apochromat. 2 mm.

The small clearer areas represent fungoid elements. The darker substance represents the hyaline embedding substance.

[1] All of the figures are photomicrographs from original specimens.

FIG. 9.—Black granule with mycelial growth proceeding from it. Zeiss a_2. Culture in bouillon.

FIG. 10.—Showing structure and appearances of the hyphæ of the mycelium obtained from the granules. Zeiss apochromat. 4 mm.

FIG. 11.—Two bouillon cultures showing the powder puff-ball appearance. In one the black granule is seen in the centre of the growth.

FIG. 12.—Potato culture of the hyphomycete obtained from the granules. The black globules are composed of a dark-brown fluid.

Fig. 1.

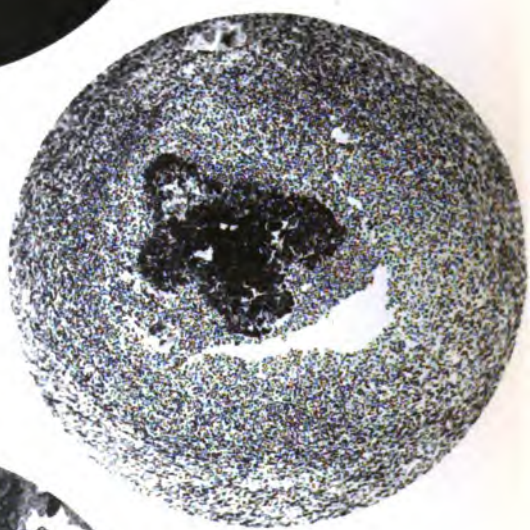

Fig. 3.

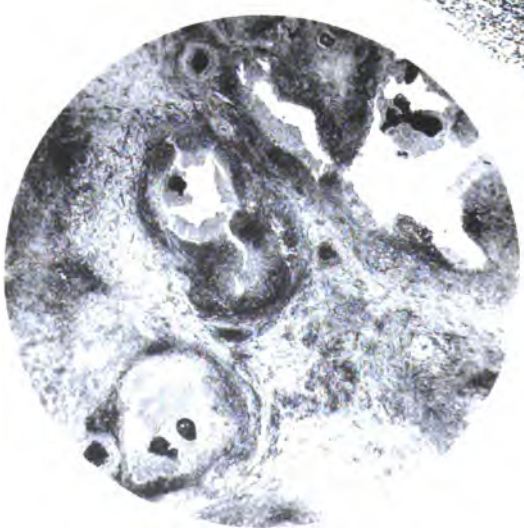

Fig. 2.

Wright—Madura Foot.

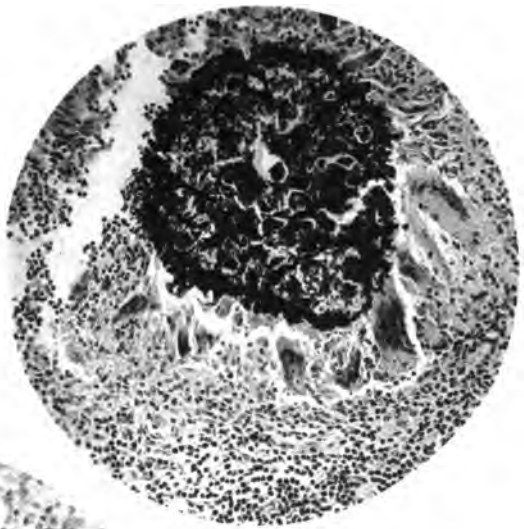

Fig. 5.

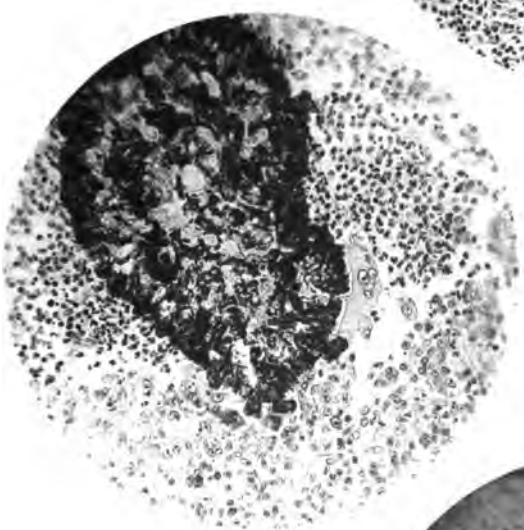

Fig. 4.

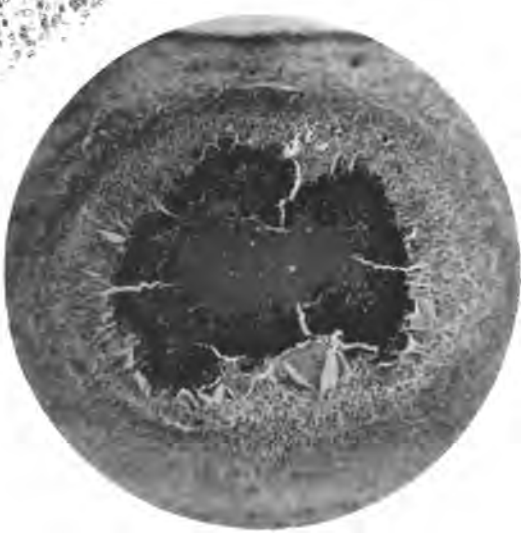

Fig. 6

THE HELIOTYPE PRINTING

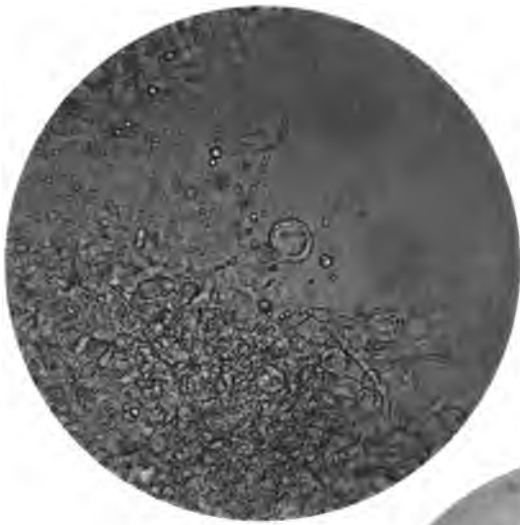

Fig. 7.

Fig. 9.

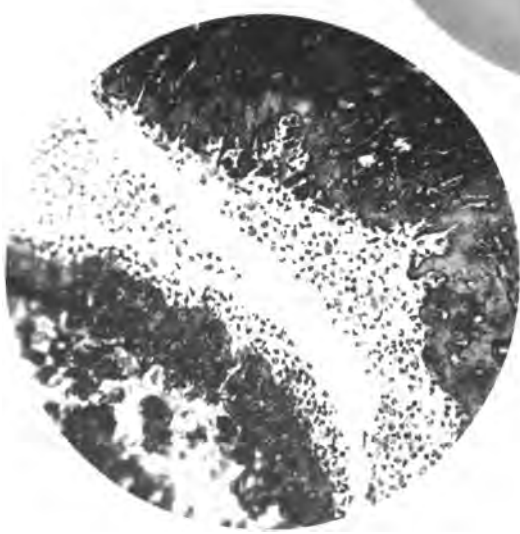

Fig. 8.

ight — Madura Foot.

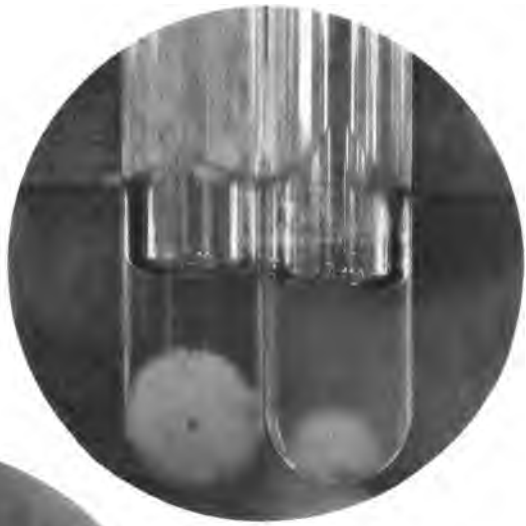

Fig. 11.

Fig. 10.

Fig. 12

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